A STUDY ON CLINICAL PROFILE AND EXTRARENAL MANIFESTATIONS OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

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DECLARATION

I solemnly declare that this dissertation entitled "**A STUDY ON CLINICAL PROFILE AND EXTRARENAL MANIFESTATIONS OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE"** was done by me at Madras Medical College & Govt. General Hospital during 2008-2011under the guidance and supervision of **Prof.K.SIVASUBRAMANIAN, M.D.** This dissertation is submitted to The Tamilnadu Dr.M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D degree in General Medicine.

Place: Chennai-3.

Date: Signature of the candidate

CERTIFICATE

This is to certify that the dissertation entitled, "**A STUDY ON CLINICAL PROFILE AND EXTRARENAL MANIFESTATIONS OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE"** submitted by Dr.Hemalatha.S, in partial fulfillment for the award of the degree of Doctor of Medicine in General Medicine by the Tamilnadu Dr.M.G.R. Medical University, Chennai is a bonafide record of the work done by her in the Institute of Internal Medicine, Madras Medical College, during the academic year 2008-2011.

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CONTENTS

Introduction

INTRODUCTION

Polycystic kidney disease is characterized by development of multiple cysts within the kidneys in bilateral fashion. A cyst is defined as a fluid filled sac lined with a single layer of fluid filled tubular epithelium. Renal cysts may develop at any location along the renal tubule from the glomerular capsule to the collecting duct by heritable, developmental or acquired processes. Single or simple renal cysts are acquired ,occur commonly in people older than 50 years of age, and are not associated with any disease.

If cysts are solitary or infrequent, they must be distinguished from haematoma or abscess, occasionally also from malignancy, particularly lymphoma.

ADPKD is the most common mendelian disorder of the kidney affecting all ethnic groups world wide with an incidence of approximately 1 in 500-1000 births.

The heritable polycystic kidney diseases are autosomal dominant and autosomal recessive disorders. The autosomal dominant disorders include three systemic diseases:

1. Autosomal polycystic kidney disease

2.Tuberous sclerosis complex

3.Von hippel -lindau disease

The major recessive disorder is autosomal recessive polycystic kidney disease. Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the fourth common cause of chronic renal failure throughout the world. It accounts for 8-10% of cases of End stage Renal Disease(ESRD). ADPKD can manifest in fetuses, new borns or young children and is the most common of the heritable polycystic kidney disease[1].

ADPKD is a systemic hereditary disorder transmitted in an autosomal dominant manner with virtually complete penetrance of the abnormal genes. Positive family history is present in 60% of patients.It is also the most frequent life threatening hereditary disease affecting 1in 500 and 1 in 1,000 live births[2]. It occurs worldwide and in all races and ethnic groups.

ADPKD can occur in fetuses, new borns, young children. But ARPKD remain undiagnosed until young adulthood. It is often evident on ultrasound imaging in children, becomes symptomatic in young adulthood ,progresses to end stage renal failure over a period of

in 50-75% of affected people. By contrast, ARPKD is most often discovered in the first year of life and terminates in end stage renal failure, in childhood or young adulthood .

Both kidneys are affected in bilateral and symmetrical fashion. The kidneys are enlarged in size as the disease progresses. In patients less than 18-29 years old with a positive history of ADPKD, the presence of two cysts, either unilateral or bilateral and in patients 30-59 years old with a positive history of ADPKD atleast two cysts in each kidney $\geq$60 years atleast four in each kidney is sufficient to make the diagnosis.

In the absence of a family history of ADPKD, bilateral renal enlargement and cysts with or without hepatic cysts and absence of other manifestations suggesting a different renal cystic disease provide presumptive evidence for the diagnosis. Contrast enhanced CT and MRI provide better anatomic definition than ultrasound and are more helpful to ascertain the severity and prognosis of the disease .

The major symptoms that cause those patients not detected by family screening to seek medical attention are hypertension, flank pain, urinary tract infection, hematuria, nephrolithiasis. Each of these symptoms may manifest in 20-30% of patients.

Several risk factors for the progression of the functional renal disease also have been identified including gender, race, age, renal volume, proteinuria, hematuria, hypertension, and LVMI. Among these risk factors the most readily treatable factor is the hypertension associated with ADPKD. Hypertension is the most important symptom present in 92% of patients at initial presentation .The hypertension in ADPKD patients occurs at a mean age of 30 years and is associated with a substantial incidence of left ventricular hypertrophy (LVH). Since cardiovascular events are the most common cause of death in ADPKD patients, the occurrence of hypertension and LVH are extremely important cardiovascular risk factors for ADPKD patients. It has been suggested that the presence of hypertension and the size of the cystic kidneys are determinants of the progression of the renal functional loss. Cardiovascular abnormalities are the important extrarenal manifestations of ADPKD[3]. These patients have increased incidence of valvular abnormalities such as mitral prolapse, aortic incompetence and tricuspid prolapse. Aortic aneurysms may also occur with increased frequency in ADPKD. Thus careful attention to the cardiac examination is warranted in ADPKD patients and standard prophylaxis to prevent subacute bacterial endocarditis should be carried out in family members with valvular abnormalities.

Hepatic cysts arise from dilatation of biliary microhamartomas and from prebiliary glands. Other uncommon manifestations are pancreatic, splenic, seminal vesical cysts and inguinal hernias. Bladder cysts,arachnoid membrane cysts, spinal meningeal diverticula are present in 10-40% of asymptomatic patients with ADPKD[4].

The major concern in any young patient with ADPKD presenting with a stroke is subarachnoid hemorrhage. An association between the two conditions has been known for many years. Recent data from a population of patients with ADPKD suggest that 12% of all affected patients died from a neurologic event, 6% of them from a subarachnoid hemorrhage . Data on the prevalence of unruptured cerebral aneurysms are more difficult to obtain, but will gradually improve as more widespread screening is undertaken. In a large autopsy series, unruptured intracranial aneurysms were identified in 4% of patients with ADPKD who died from unrelated causes . Although this rate is higher than that in the general population, the difference was not significant. Asymptomatic intracranial aneurysms can be identified with either thin-section CT scanning or magnetic resonance angiography (MRA). Combined data from three large prospective studies suggest a prevalence of approximately 8% in the ADPKD population; this figure doubles in ADPKD patients who have a family history of intracranial

aneurysm . Morbidity and mortality after rupture of an aneurysm are high. In the autopsy series from the Mayo Clinic, mortality six months after rupture was 55% , although in a more selected European population, overall mortality was 10%, but 43% of those surviving beyond three months after rupture had severe neurologic disability . The most important determinant of whether an aneurysm will rupture appears to be its size. In a series of otherwise normal patients with unruptured cerebral aneurysms followed for eight years, all the ruptures occurred when the aneurysm was greater than 10 mm in diameter . Similar data are not yet available for a population of ADPKD patients, but prospective studies are currently underway.

About 40% of affected members initially deny a family history but on careful examination perhaps, only 10% lack an affected family relative. Inadequate patient education still represent an impediment to early disease detection, genetic counselling and timely treatment of disease complications.

In view of diverse clinical presentations and complications of ADPKD, we conceptualized a study to analyse extrarenal manifestations of ADPKD in our indigenous population.

Aim of the Study

AIMS AND OBJECTIVES

1. To document various clinical presentations of ADPKD.

2. To analyse various extrarenal manifestations of ADPKD in our native population

Review of Literature

REVIEW OF LITERATURE

Since autosomal dominant polycystic kidney disease (ADPKD) is one of the most common genetic abnormalities seen in today's medical practice, many internists are likely to treat patients affected by this condition.Genetic abnormalities have been increasingly recognized, and the pathophysiology of the disease is beginning to be unravelled. Because of advances in imaging technology, surrogate markers for disease progression have allowed clinical studies of newer therapeutic agents to proceed. In the near future, therapies for this common genetic disease may be available to either prevent or stabilize the disease course for many affected individuals.

ADPKD is a systemic hereditary disorder transmitted in an autosomal dominant manner. It is genetically heterogenous. The systemic manifestations include cystic and non-cystic renal and extrarenal abnormalities[4,6,7]. Renal cysts occur in 100% of gene carriers[1].

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the fourth common cause of chronic renal failure throughout the world[6]. Progressive expansion of multiple, bilateral renal cysts lead to massive

enlargement of kidneys and to progressive renal failure. Although renal cysts and renal failure are the cardinal manifestations of ADPKD, it is a systemic disorder with multiple extrarenal manifestations encompassing both cystic involvement of other organs and connective tissue abnormalities. The observation that only one half of ADPKD population reaches End stage renal disease(ESRD) by the middle of 6th decade[8,9] and the dialysis survival for patients with ADPKD surpasses that of general dialysis population[10,11]suggest that the extrarenal manifestations of ADPKD have ample time to produce clinical complications.

GENETICS

During the past fifteen years an enormous amount of effort has been invested in exploring the functions of the PC1 and PC2 proteins. The return on this investment constitutes something of an embarrassment of riches, in that the polycystin proteins appear to participate in a nearly bewildering array of signaling pathways and regulatory processes, and to reside within a complex collection of subcellular structures.

A major goal of current ADPKD research is to elucidate the connections between these cell biological properties of the polycystin

proteins and the pathogenesis of the disease that develops when their expression is perturbed. One of the most intriguing discoveries to emerge from this intense research is the realization that portions of the cellular populations of PC1 and PC2 localize to the primary cilium. ADPKD is the founding member of the "ciliopathies," a recently defined class of genetic disorders that result from mutations in genes encoding cilia-associated proteins. These disorders are often characterized by the presence of renal cysts as well as by additional pathologies including neural tube defects, retinal malformations, and polydactyly[12]. Although the cellular and molecular mechanisms responsible for the pathogenesis of ADPKD are still very much the subject of spirited and healthy debate, it has become clear in recent years that understanding ADPKD, and the function or dysfunction of PC1 and PC2, will require an appreciation of these proteins' roles in the primary cilium.

Recent advances in the molecular genetics of ADPKD include the discovery of multiple genetic loci – PKD1 in chromosome 16[13]; PKD2 on chromosome 4 [14,15] and atleast one additional site unlinked to chromosome 4 or chromosome 16[16].

ADPKD is thought to be an example of a “second hit” phenomenon. An individual inherits a mutated polycystic kidney disease gene from one of his or her parents. The wild-type or normal allele in individual cells may then be affected by a so-called “second hit” allowing this cell to proliferate and form individual cysts . No more than 5% of nephrons are thought to be involved in cystic change, but the genetic mutation is obviously present in all cells. Some manifestations of ADPKD, such as intracranial aneurysms, also persist in families.

PATHOPHYSIOLOGY AND PATHOBIOLOGY

Cystic kidneys usually maintain their reniform shape. Their size ranges from minimally or moderately enlarged in early disease to more than 20 times the normal size in advanced disease. Although unusual, striking asymmetry of cyst development may be seen. Both the outer and the cut surfaces show numerous cysts ranging in size from barely visible to several centimeters in diameter. They are distributed evenly throughout both the cortical and medullary parenchyma.

Polycystin 1 and 2, the gene products of PKD1 and PKD2 are plasma membrane proteins that form components of a novel multifunctional signaling pathway[17]. These polycystin proteins are

situated within the cell in areas involving the primary cilium. Thus, mutated polycystins are an example of a ciliopathy. The cilia's function is to transmit mechanosensory signals into the cell controlling cell growth and proliferation. Polycystin 1 is predicted to have a receptor like structure and may be involved in cell-cell and/or cell-matrix interaction. By contrast, polycystin 2 is thought to function as a subunit of a non-selective cation channel. Both proteins have been to interact invitro through their cytoplasmic region and transmit fluid-flow mediated mechanosensation by the primary cilium in renal epithelium[17,18]When the polycystins are mutated, a complex series of events ensues. Disruption of the function of polycystin 1 or 2 may cause ADPKD, owing to the inability of the tubular epithelial cells to sense mechanical cues that normally regulate tissue morphogenesis[18] leading to growth of individual cells and then to the formation of a fluid-filled cyst . As the cyst gradually enlarges, it becomes pinched off from the nephron of origin. Because fluid secretion continues, the result is a gradually enlarging cystic kidney with an increased volume. The renal parenchyma may also show abnormalities, but the primary pathophysiologic process of the cystic kidney is a gradually enlarging kidney with an increase in renal volume.

Although ADPKD is genetically dominant at the organismal level, it is recessive at the cellular level. The kidneys of an ADPKD patient who inherits one mutated copy of PC1 or PC2 from a parent will develop and function normally into adulthood. Over time, however, cysts will form in this patient's kidneys and several studies suggest that the cells that line these cysts will have lost both functional copies of a polycystin gene. This indicates that an additional "second hit" somatic mutation may cause cysts to form. According to this model, each cyst arises as a consequence of a distinct somatic mutation event, explaining the disease's slow progression over the course of decades. Subtle factors may also impact upon disease progression, including the level of PKD1 protein expression, the penetrance of pathogenic alleles, and the stage of kidney development affected by *PKD1* mutation .The slow accumulation of cysts throughout adult life may be due to slow accumulation of inactivating "second hit" mutations as a result of a constant somatic mutation rate. It is also possible that, as individuals age, their kidneys are more likely to suffer transient obstructive or ischemic injuries to the tubule epithelial cells. These injuries would then stimulate repair, which involves cellular growth and division. Given the importance of PC1 and PC2 for cellular growth and differentiation, the decreased levels of functional polycystin proteins present in the cells of

individuals heterozygous for ADPKD mutation could perturb the repair process and thus lead to cyst formation.

CYST EXPANSION

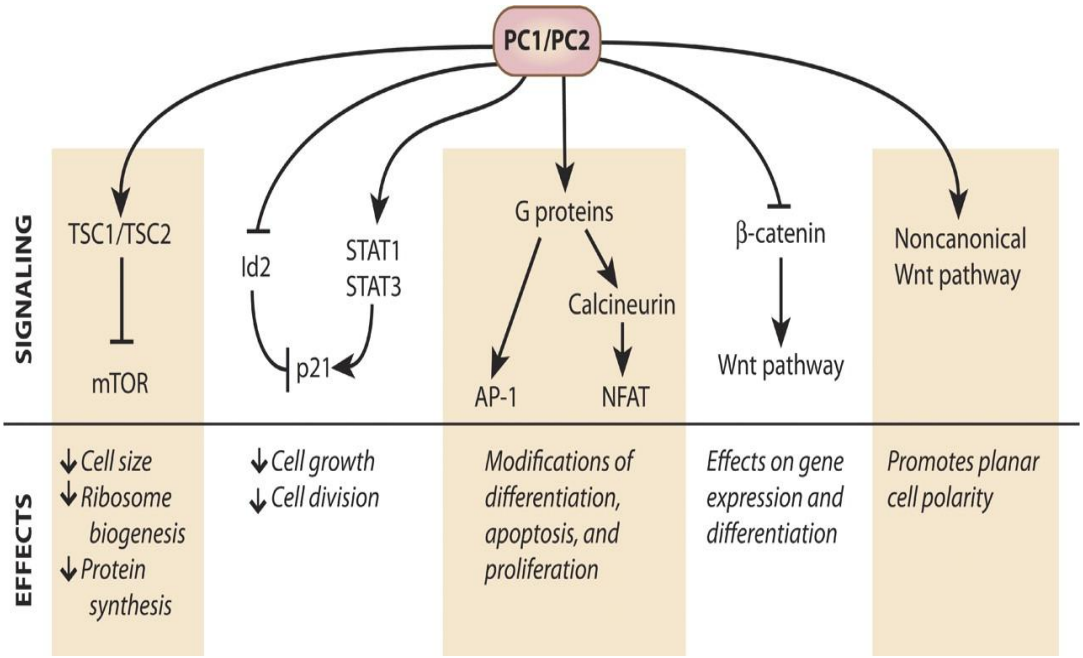
The macroscopic consequence of ADPKD progression is the formation of fluid- filled cysts, which constitute a stark contrast to the normally compact arrangement of tubules in a healthy kidney. At the cellular level, this transformation is predicated upon two alterations: cells must organize themselves to create spherical rather than tubular structures, and the lumens of these structures must fill with fluid in order to expand the consequent cysts.

The other critical aspect of cyst formation, which involves the expansion of cyst fluid volume, can be understood as the conversion of the cyst-lining cells from an ion-absorptive to an ionsecretory epithelium. Ion secretion into the lumen then drives paracellular or transcellular osmotic water movement into the cyst. A prime component of this secretion is Cl^-transport stimulated by cAMP. The fluid movement driving cyst formation is stimulated by cAMP and involves the apical cystic fibrosis transmembrane regulator (CFTR) and the

basolateral Na+-K+-2Cl ¯ cotransporter. PC1 may affect the expression, localization, or activity of Cl^- channels.

Recent data have suggested that the progression of renal disease, the occurrence of hypertension and symptoms of the disease are related to kidney volume. In fact, in most cases, renal volume increases years before the glomerular filtration rate starts to decrease, making the glomerular filtration rate or its surrogate serum creatinine a poor way to follow patients with ADPKD.

EFFECTS OF PC1 &PC2 THAT AFFECT MULTIPLE SIGNALLING PATHWAYS



Disease caused by PKD2 mutations is generally milder than disease caused by PKD1 mutations,with an older age at diagnosis and later onset of hypertension and renal failure. In the reported ADPKD2 families to date onset of end stage renal failure occurred at a mean age of 70-73 years,whereas in ADPKD1 families the mean age at onset of ESRD is 53-56 years.

RENAL FUNCTION ABNORMALITIES

Impaired urinary concentrating capacity is common even at early stages. Sixty percent of children cannot maximally concentrate the urine. Plasma vasopressin levels are increased. The vasopressin-resistant concentrating defect is not explained by reduced cAMP or expression of concentration associated genes, which are consistently increased in animal models. Whether it is due to disruption of the medullary architecture by the cysts or to a cellular defect directly linked to the disruption of the polycycstin function has not been determined. Recent studies suggest that the urinary concentrating defect and elevated vasopressin levels may contribute to cystogenesis. They may also contribute to the glomerular hyperfiltration seen in children and young adults, and to the development of hypertension and chronic kidney disease progression. Defective medullary trapping of ammonia and

transfer to the urine caused by the concentrating defect may contribute to the low urine pH values, hypocitric aciduria, and predisposition to stone formation.

Reduced renal blood flow is another early functional defect.It may be due to the changes in intrarenal pressures, to neurohumoral or local mediators, or to intrinsic vascular abnormalities. Mild to moderate persistent proteinuria (150–1500 mg/day) may be found in a significant number of patients in the middle to late stages of the disease. It is an indicator of more progressive disease.

RENAL COMPLICATIONS

ADPKD patients may suffer complications such as infected cysts, cyst rupture/hemorrhage, and nephrolithiasis that often cause crippling acute renal pain.Pain is the most frequent symptom (~60%) reported by adult patients. Some patients develop chronic flank pain without identifiable etiology other than the cysts.

Acute pain may be due to

1. urinary tract infections
2. renal cyst infection/hemorrhage
3. nephrolithiasis

URINARY TRACT INFECTIONS &CYST HEMORRHAGE

Subjects were considered as having UTI if there was a history of two or more episodes of UTI. Patients were considered having gross hematuria if there was a history of observing blood macroscopically in the urine and microhematuria if the urinalysis showed up to 5 rbc/hpf.

Infected cysts can cause diffuse pain that may be unilateral or bilateral, and the pain pattern can be similar to pyelonephritis in patients with noncystic kidneys. UTIs in patients with ADPKD, however, can be much more difficult to diagnose and manage than in patients with non-cystic kidneys. UTIs occur in many patients with ADPKD and, as expected, the incidence is much higher in women than in men. Most of them were caused by enterobacteriaceae. In one report, 68% of women with ADPKD had UTIs as compared with only 19% of men. Both hematogenous spread and ascending infection are the presumed causes for cyst involvement. A sudden increase in flank pain associated with fever is the most common presentation of cyst infection. The pain pattern tends to stay in one general area without radiation, not being relieved by position change. Infected cysts may not be in communication with the draining urinary tract in patients with ADPKD

and hence the urinalysis may be relatively benign and the urine cultures can be persistently negative.

Management of upper tract infections in ADPKD may be difficult, since antibiotics may not be able to cross the epithelial lining of the cysts and produce a high enough concentration in the cyst fluid. It is imperative that these UTIs be promptly treated to prevent ongoing pain and other complications in these non communicating infected cysts such as sepsis, perinephric abscess, and subsequent renal failure. Another common cause of acute flank pain in association with gross hematuria in ADPKD is the rupture of cysts. Hemorrhage may be into a communicating urinary tract. However, it is not certain that gross hematuria represents hemorrhage into cysts communicating with the urinary tract, since most cysts derived from proximal and distal tubule segments grow as a result of aberrant tubulogenesis, and become walled off and separate from the tubules of origin by the time they become detectable by imaging studies. Gross hematuria is present in as many as 43% to greater than 50% of the patients with polycystic kidney disease. Hemorrhage into a cyst occurs without gross hematuria when there is no communication with the urinary tract. The frequency of hematuria from cyst rupture correlates directly with the size of the kidneys, the

incidence of hematuria increasing dramatically when one or both of the kidneys is larger than 15 cm. Also, hypertensive ADPKD subjects are more likely to have gross hematuria than normotensive patients. Prognostic characteristics are noted with gross hematuria; the greater the number of episodes, the worse the prognosis. Increased episodes of gross hematuria are noted in association with a higher baseline serum creatinine and episodes of bleeding before age 30 carry a worse renal outcome.

In general, the episodes of hematuria are usually self-limited, lasting two to seven days. These episodes tend to resolve spontaneously with conservative management consisting of bedrest and hydration, but persistent bleeding has been noted to occur for weeks. Pain related to cyst rupture tends to be localized and definable by finger point. However, referred pain to another location in the abdomen or up to the shoulder (for example, with right kidney cyst rupture simulating biliary colic) can occur with hemorrhage into a larger cyst, resulting in compression of surrounding structures.

It is possible for significant bleeding into the renal cysts to occur with subsequent formation of clots. This in turn may lead to urinary tract obstruction and severe renal colic. Prolonged bed rest, intravenous

hydration, heat and judicious narcotic administration are often necessary in this circumstance.

It is also possible for cysts on the surface of the kidneys to rupture and subsequent hemorrhage can result in a subcapsular hematoma. The patient may then experience a mild steady flank pain until the hematoma has been reabsorbed. Although nonsteroidal anti-inflammatory drugs (NSAIDs) may be very helpful in the case of colicky pain, they must be used cautiously and should not be the first line of treatment . Hematuria may rarely be so severe and/or persistent as to necessitate transfusion. In these cases, either nephrectomy or renal arterial embolization may be necessary to control the bleeding. Embolization, although less invasive than nephrectomy, can in itself cause severe continuous pain associated with abdominal distension. This pain is due to renal parenchymal ischemia in an enlarged kidney following embolization, and can be difficult to control with conservative management and non-opioid pharmacologic intervention.

Vascular endothelial growth factor (VEGF) produced by the cystic epithelium may promote angiogenesis, hemorrhage into cysts, and gross hematuria. Symptomatic episodes likely underestimate the frequency of cyst hemorrhage because more than 90% of ADPKD

patients have hyperdense (CT) or high-signal (MRI) cysts reflecting blood or high protein content. Most hemorrhages resolve within 2 to 7 days. Nuclear imaging (^{67}Ga or ^{111}In-labelled leukocyte scans) may be helpful, but false-negative and false-positive results are possible. Cyst aspiration should be considered when the clinical setting and imaging are suggestive and blood and urine cultures are negative. It may follow strenuous physical activity or minor trauma but often occurs spontaneously. If hematuria is recurrent or persists for more than two weeks and the patient has other risk factors associated with the development of renal malignancies, then the possibility of neoplasm should be investigated. Treatment of hematuria secondary to cyst rupture consists of rest, hydration and analgesics.Renal cell carcinoma (RCC) is a rare cause of pain in ADPKD.

NEPHROLITHIASIS

Patients with nephrolithiasis were defined as those with calculi within the collecting system of the kidney on ultrasound with or without a clinical history of stones. Criteria for the sonographic diagnosis of calculus included identification of an echogenic focus with posterior acoustic shadowing within the kidney but outside an identifiable cyst. Calculi associated with cyst walls were not considered as calculi.

Renal colic caused by kidney stones, another complication of ADPKD, occurs in about 20% of patients with ADPKD. When considering the spectrum of both symptomatic and asymptomatic stones, about a third of the ADPKD patients have nephrolithiasis. This much higher incidence of nephrolithiasis than in the general population is a cause of significant morbidity in ADPKD patients because of flank pain, hematuria and urinary tract infection. The prevalence of renal calcifications, which represent stones within the collecting system, interstitial calcifications, or calcifications within cysts, was found to be 50% by CT in a study by Levine and Grantham. While patients with ADPKD develop a variety of kidney stones (calcium oxalate, calcium phosphate, calcium carbonate, struvite), uric acid stones are more common in polycystic kidney disease patients as compared to the incidence in the general population, accounting for up to 50% of the calculi formed.

Mechanisms responsible for the increased association between ADPKD and nephrolithiasis remain conjecture. Patients with ADPKD may be predisposed to stone formation either because of a metabolic defect(decreased ammonia excretion, low urinary PH and low urinary citrate concentration), structural abnormality secondary to cyst growth,

renal tubular stasis, or a combination of these factors. It is noted that approximately 50% of ADPKD patients have hypocitraturia. Renal function of adult ADPKD patients with kidney stones is significantly worse than in patients without stones. ADPKD stone formers have larger predominant cyst size compared to non-stone formers. Increased cyst number also is associated with stone formation. Therefore, anatomic deformity related to cyst number, size, and growth may contribute to the formation of kidney stones, possibly through a mechanism of increased urinary stasis. Because of the compressed and distorted renal calices, treatment modalities such as ureteroscopy, extracorporeal shock wave lithotripsy (ESWL), and nephrolithotomy are more difficult in patients with ADPKD. Since these therapeutic and palliative procedures may not be as efficacious, ADPKD patients may have to endure prolonged and repeated episodes of renal colic while undergoing medical management addressed towards the etiology of the stone formation. A rapidly progressive distension produced by stone movement usually causes a much more severe pain than a slowly increasing distension. Thus, it is critical that pain control be adequately addressed while a detailed evaluation is underway. Renal prostaglandins may be a major contributing factor in the symptom complex known as renal colic. Acute ureteral obstruction by a stone can increase renal

pressure, leading to a release of inflammatory mediating renal prostaglandins. These prostaglandins, especially prostaglandin E_2 (PGE_2), cause vasodilation of the afferent arterioles in the kidney and inhibition of antidiuretic hormone (ADH), with a resultant diuresis and a further increase in renal pressure. Thus, a vicious cycle may be established.

A CT of the abdomen before and following contrast enhancement is the best imaging technique to detect small uric acid stones that may be very faint on plain films with tomograms and to differentiate stones from cyst wall and parenchymal calcifications. Stones may be missed if only a contrast-enhanced CT is obtained.

EXTRARENAL MANIFESTATIONS

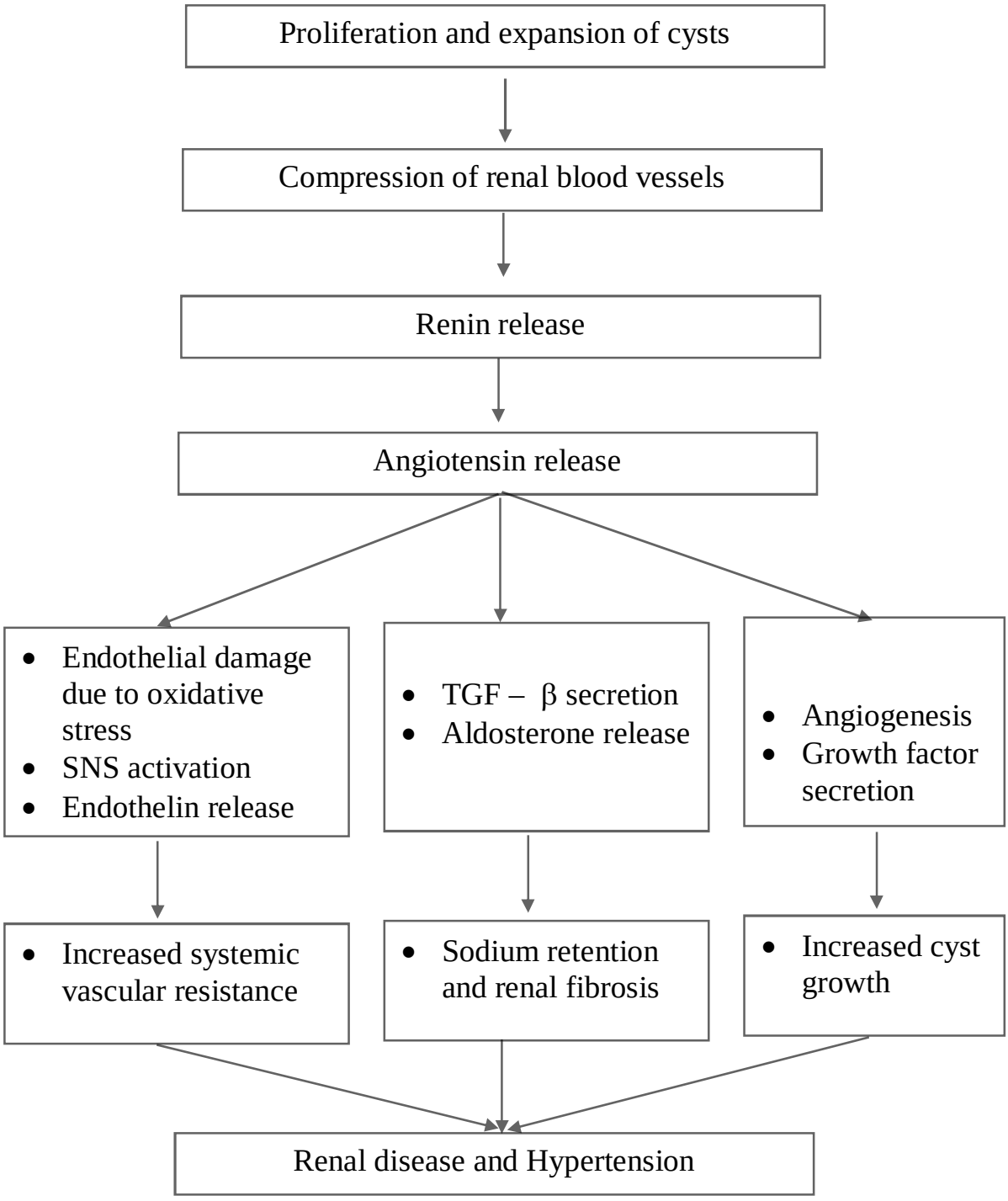
CARDIOVASCULAR MANIFESTATIONS

The disease is characterized by renal and extrarenal involvement with cystic and noncystic manifestations. With the availability of renal replacement therapies for patients with end-stage renal disease (ESRD), cardiovascular complications have emerged as a major cause of death in patients with ADPKD.[19] Hypertension is a common early finding and can be the symptom that leads to the diagnosis of ADPKD.[20]

Hypertension is also associated with a rapid progression to ESRD and increased cardiovascular complications. Left ventricular hypertrophy (LVH), which is an important risk factor for premature cardiovascular death, occurs frequently in patients with ADPKD. Aneurysms and cardiac valvular abnormalities are other cardiovascular manifestations of this disease.

Hypertension is very common in ADPKD, and occurs in 50–70% of patients before any substantial reduction in glomerular filtration rate is observed.[20]Furthermore, hypertension occurs at a much earlier age in patients with ADPKD than in the general population.[21]The median age at diagnosis of hypertension in ADPKD was 32 years for males and 34 years for females,[22] compared with a median age of 45–55 years in patients with essential hypertension. Studies have reported that hypertension occurs in 20–30% of children with ADPKD.[23]Moreover, Schrier *et al*.[23] demonstrated that the likelihood of hypertension in both men and women with ADPKD was significantly greater when the affected parent was hypertensive. Thus, the presence of hypertension in the ADPKD-affected parent of a patient with ADPKD should alert the clinician to the need for early detection and treatment of hypertension.

Potential pathogenetic mechanism of HT in ADPKD



SNS - Sympathetic Nervous System
TGF – Transforming growth factor

ROLE OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Renal structural changes have an important role in the pathogenesis of hypertension in patients with ADPKD. Gabow *et al*. reported that adult patients with ADPKD and hypertension had significantly greater renal volume than patients with normal blood pressure. These findings suggest that activation of the renin-angiotensin-aldosterone system (RAAS) as a result of cyst expansion and local renal ischemia has an important role in the development of hypertension in this disease. Immunohistochemical studies of nephrectomy specimens from patients with ADPKD have shown hyperplasia of renin-secreting cells of the juxtaglomerular apparatus, which suggests chronic stimulation of the RAAS is present. In addition, high levels of renin were found in cyst fluid obtained from patients with ADPKD. Loghman-Adham *et al*. showed that other components of the RAAS, including angiotensinogen, angiotensin-converting enzyme (ACE), angiotensin II receptor and angiotensin II peptide were also present in the cysts and dilated tubules of ADPKD kidneys. Activation of the RAAS in ADPKD has been confirmed by the demonstration that plasma renin activity and aldosterone concentrations in the supine and upright positions, as well as after Captopril administration, are greater in

patients with ADPKD, hypertension and normal renal function than in patients with essential hypertension who are of the same age, sex, body surface area, sodium excretion, renal function and mean arterial pressure. Studies have also shown that administration of ACE inhibitors decreases mean arterial pressure, renal vascular resistance and filtration fraction significantly more in hypertensive patients with ADPKD than in healthy controls with normal blood pressure. Total exchangeable sodium, plasma renin activity and plasma aldosterone levels were significantly higher in these patients than in family members of the same age and sex. Similarly, reported that during chronically high sodium intake, plasma renin activity was higher in patients with ADPKD who had normal blood pressure and creatinine clearance greater than 70ml/min/1.73m^2 than in unaffected controls from the same families. These findings suggest that the RAAS is activated at an early stage of ADPKD, and this activation precedes hypertension and the major clinical manifestations of the disease.

Twenty-four-hour ambulatory blood pressure monitoring of children or young adults without hypertension may reveal elevated blood pressures, attenuated nocturnal blood pressure dipping, and exaggerated blood pressure response during exercise, which may be

accompanied by left ventricular hypertrophy and diastolic dysfunction. Early detection and treatment of hypertension is important because cardiovascular disease is the main cause of death

ROLE OF OTHER FACTORS

Although activation of the RAAS seems to have a major role in the pathogenesis of hypertension in ADPKD, other factors might also be involved. Harrap et al demonstrated that muscle sympathetic nerve activity was increased in hypertensive patients with ADPKD regardless of renal function, which suggests that sympathetic hyperactivity could contribute to the pathogenesis of hypertension in this disease. Of note, the RAAS is stimulated by increased sympathetic activity, and angiotensin stimulates the sympathetic nervous system.

Plasma vasopressin levels correlate with blood pressure levels in salt-sensitive forms of human and experimental hypertension. Since plasma vasopressin concentrations are increased in patients with ADPKD, vasopressin could also contribute to the development of hypertension in this disease; however, this theory remains to be proven.

The cystic epithelium of kidney sections from patients with ADPKD exhibits increased expression of endothelin 1. Endothelin 1 is

also found in the cyst fluid. Patients with ADPKD have higher plasma levels of endothelin 1 than do healthy controls and patients with essential hypertension. Moreover, endothelium-dependent relaxation is impaired and endothelial nitric oxide synthase activity is decreased in patients with ADPKD. These findings suggest that endothelial dysfunction secondary to impaired release of nitric oxide exists in these patients. An imbalance in endothelium-derived vasoactive mediators (that is, endothelin and nitric oxide) might, therefore, contribute to the pathogenesis of hypertension in ADPKD. In a 2008 study, Wang et al.[24]investigated asymmetric dimethylarginine (ADMA) as a marker of nitric oxide synthase inhibition and the lipid peroxidation product 13-hydroxyoctadecadienoic acid as a marker of oxidative stress in patients with early ADPKD. The investigators found that these patients had significantly increased plasma ADMA and plasma 13-hydroxyoctadecadienoic acid levels and significantly decreased urinary clearance of ADMA compared with healthy controls. Demonstration of endothelial dysfunction and increased carotid intima-media thickness in both hypertensive and normotensive patients with ADPKD and well-preserved renal function shows that atherosclerosis starts very early in the course of this disease.[25]

The findings of early-onset endothelial dysfunction mentioned above were confirmed by a study that reported decreased coronary flow velocity reserve—which represents the capacity of the coronary circulation to dilate after an increase in myocardial oxygen demand—in both hypertensive and normotensive patients with ADPKD. Furthermore Borresen et al. investigated arterial stiffness in early ADPKD by pulse-wave analysis and measurement of pulse-wave velocity. They found that pulse-wave reflection was amplified even in young patients with ADPKD who have normal blood pressure and renal function, which demonstrates that pathological changes in the arterial system occur early in the course of disease. The stimulation of angiotensin II and the sympathetic nervous system secondary to hyperinsulinemia might contribute to increased LVMI in patients with PKD1.

ANEURYSMS

Patients with ADPKD have a greater prevalence of intracranial aneurysms than the general population (4.0–11.7% versus 1.0%). Ruptured intracranial aneurysms account for 4–7% of deaths in patients with ADPKD and such deaths occur at a younger age than in the general population. Aneurysmal involvement of extracranial arteries, such as the coronary arteries, abdominal aorta, renal artery and splenic artery has

also been reported in patients with ADPKD. Other reported vascular manifestations of ADPKD are dolichoectasias (elongations and distentions of the arteries caused by weakening of the vessel walls) and dissections. Since polycystin 1 and polycystin 2 are both expressed in vascular smooth muscle cells, interactions of these proteins with a single pathway might have a role in the pathogenesis of aneurysms in ADPKD.

The early and effective treatment of hypertension is also important for the prevention of cardiovascular complications in ADPKD. Antihypertensive treatment with an ACE inhibitor reversed LVH over a 7-year follow-up period, which decreased an important risk factor for cardiovascular death in patients with ADPKD. A 7-year prospective, randomized study in 75 hypertensive patients with ADPKD and LVH compared the effects of rigorous and standard blood pressure control (<120/80 mmHg versus 135–140/85–90 mmHg) on LVH and renal function. Both strategies decreased LVH significantly; however, rigorous blood pressure control was significantly more effective in decreasing LVMI than was standard blood pressure control. In addition, significantly more patients in the rigorous-control group (71%) than in the standard-group (44%) achieved normal LVMI. A subgroup analysis showed that patients who received the ACE inhibitor enalapril

experienced a significantly greater decrease in LVH than patients who received the calcium-channel blocker amlodipine, despite similar blood pressure control. A blood pressure goal of less than 120/80 mmHg and the use of an ACE inhibitor is, therefore, recommended for patients with ADPKD who have hypertension and LVH.

HEPATIC CYSTS

Hepatic cysts are the most common extrarenal manifestation of ADPKD in 10 to 88% [26,27,28]of patients. This high variability is probably due to increasing prevalence of hepatic cysts with age. Cysts are detectable in only 10-17% of patients below age of 40 years and 70-75% of patients older than age of 60 years.[26,29,30]. Hepatic cysts are found in 60-75% of ADPKD patients with ESRD who are on or approaching dialysis [27,31].Hepatic cyst disease is most severe in patients with the most severe renal cystic disease and the worst renal function [31]; hepatic cysts are found in 60% to 75%.

The prevalence of hepatic cysts in nonazotemic subjects is similar for men and women; However severe hepatic cystic disease that is increases number and size of cysts, primarily affects women, particularly those who have had multiple prergnancies (or) exposure to

exogenous female sex steroids[27]. By contrast to this female predominance of severe hepatic cystic disease, females with ADPKD are not at greater risk for severe renal cystic disease; in fact male ADPKD patients have a faster rate of decline in Glomerular Filtration Rate(GFR) than do females.

Isolated polycystic liver disease (that is, in the absence of renal cysts) is a separate hereditary disorder that appears to be unrelated to ADPKD. Genetic linkage studies document an absence of linkage to the known ADPKD loci on chromosomes 4 and 16 .

Risk factors for the development of hepatic cysts in ADPKD are

1) Increasing age
2) Increasing severity of renal cystic disease
3) Decreased creatinine clearance
4) The number and size of hepatic cysts correlated with the occurrence of pregnancy and number of pregnancies
5) Female gender

Liver function is well preserved and liver enzymes, bilirubin usually remain normal in both male and female patients[32,33]. The preservation of liver function in ADPKD patients with hepatic cysts was

explained by a careful study done in women with massive hepatic cystic disease that revealed preservation of a normal volume of hepatic parenchyma despite a large number and volume of cysts

Complications of Hepatic cysts

Fever, leucocytosis and right upper quadrant pain are the typical symptoms of hepatic cyst infection. These symptoms could also arise from infection of one or more renal cysts. It is usually monomicrobial and caused by enterobacteriaceae.Hepatic cyst infections frequently elevate AST, ALP or bilirubin. Since uncomplicated hepatic cysts usually don't elevate liver enzymes or biliubin enzymes, this finding can help distinguish hepatic from renal cyst infection. Ultrasonogram seems first choice among imaging technique to detect hepatic cyst. If unsuccessful, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) is indicated[32]. MRI sensitively differentiates between a complicated and an uncomplicated hepatic cyst. On CT scanning, fluid-fluid levels within cysts, cyst wall thickening, intracystic gas bubbles, and heterogeneous or increased density have been associated with infection. Radionuclide imaging and more recently ^{18}F-fluorodoxyglucose positron emission tomography scanning have

been used for diagnosis. Infection usually affects patients with massive hepatic cyst development[31,32,38].

Symptoms typically caused by massive enlargement of the liver or by mass effect from a single or a limited number of dominant cysts include dyspnea, early satiety, gastroesophageal reflux, and mechanical low back pain. Rare complications of massive ADPKD hepatic cystic disease include obstructive jaundice[35,36,37], portal hypertension with oesophageal varices[33,38]and obstruction of hepatic venous outflow[34,40]. These complications are thought to be due to compression of biliary or vascular structure respectively by a single dominant cyst or multiple cysts.

A small number of patients, mostly women, develop disabling abdominal pain and distention secondary to massive hepatomegaly from large numbers and volume of hepatic cysts. Partial hepatectomy, surgical fenestration, percutaneous drainage, or alcohol sclerosis of several dominant cysts may be required to palliate such symptoms[39]

Congenital hepatic fibrosis, frequently associated with Autosomal Recessive Polycystic Kidney. Disease also affects a small number of families with typical ADPKD[41]. Hepatic cysts in patients

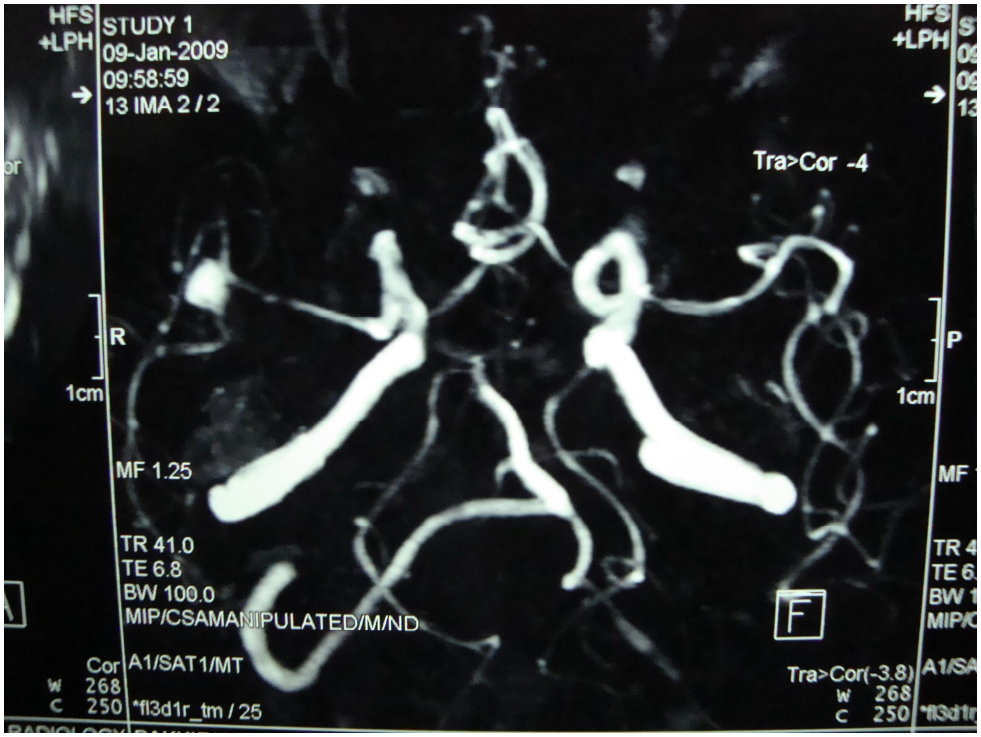
with ADPKD derive from intrahepatic biliary epithelium. Cysts grow as a result of progressive dilation of biliary ductules in Von Meyenburg complexes or biliary hamartomas, which e ventually separate from the ductule of origin[42,43].

CYSTS IN OTHER ORGANS

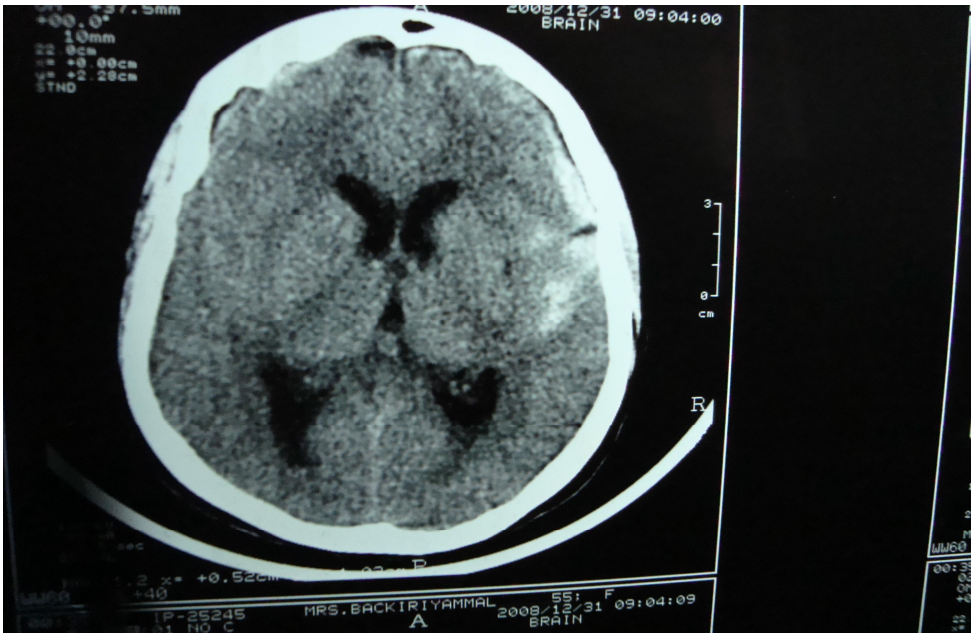
Cysts are found in pancreas in approximately 5%, arachnoid in approximately 8%, and seminal vesicles in approxi-mately 40%. Seminal vesicle cysts rarely result in infertility. Defective sperm motility is another cause of male infertility in ADPKD. Pancreatic cysts are almost always asymptomatic, with very rare occurrences of recurrent pancreatitis. It is uncertain whether the reported association of carcinoma of the pancreas represents more than chance. Arachnoid membrane cysts are asymptomatic but may increase the risk for subdural hematomas. Spinal meningeal diverticula may occur with increased frequency and rarely present with intracranial hypotension due to cerebrospinal fluid leak. Ovarian cysts are not associated with ADPKD.

INTRACRANIAL ANEURYSM

MRI BRAIN SHOWING ICA IN A PATIENT WITH ADPKD



NON ENHANCED CT BRAIN OF THE SAME PATINT SHOWING SUBARACHNOID HEMORRHAGE



INTRACRANIAL ANEURYSM

Rupture of an intracranial aneurysm (ICA) is one of the dreadest complications of ADPKD. Autopsy series, case reports and prospective imaging studies provide strong support for the relationship between ICA and ADPKD[44-48], but questions remain as to the exact prevalence of ICA, the identification of patients at high risk of rupture, and whether screening and prophylactic repair should be performed in asymptomatic patients with small ICAs. The reported frequency of ICA ranges from 0% to 41% . The latter speculation is supported by the observation that ICAs tend to cluster within families . Most ICAs occur in the anterior circulation. Recent prospective imaging studies of asymptomatic subjects using high-resolution computerized tomographic or magnetic resonance imaging techniques with or without four-vessel cerebral angiography found ICAs in 0% to 11% of subjects all ICAs found in these studies were less than 7 mm in size .[45-48]

Intracranial aneurysm produces symptoms via three mechanisms: compression of adjacent structures, focal brain ischemia due to embolism, and subarachnoid hemorrhage due to rupture. Urgent neurologic or neurosurgical consultation should be obtained for ADPKD patients with any new, severe, or focal neurologic symptoms, including

headache. Rupture of an ICA is a catastrophic event, with mortality approaching 50% and devastating morbidity affecting 50% of the survivors. Kaehny and Everson suggested that patients with ADPKD have a greater mortality rate from ICA rupture because of a greater prevalence of renal insufficiency and hypertension than do patients without

ADPKD however, when data derived from post-mortem studies are excluded, the mortality rate is similar to that in the population without ADPKD[49] . Intracranial aneurysms rupture at an earlier age in patients with ADPKD. Of reported ruptured ICAs in patients with ADPKD, 64% to 80% occurred before age 50, whereas in patients without ADPKD, rupture of ICAs occurred in only 40% to 45% before age 50. Neurosurgical intervention for ruptured ICA is done primarily to prevent recurrence of bleeding; few patients require evacuation of a space-occupying hematoma to improve outcome. Rupture of an ICA is only one of multiple diagnostic possibilities that must be considered when evaluating an acute neurologic event in a patient with ADPKD. Much more likely are cerebral complications due to hypertensive cerebral hemorrhage or cerebral ischemia and infarction[50,51] . The catastrophic outcome of ruptured ICA has prompted extensive

discussion of the risks and benefits of screening and prophylactic repair of ICA in asymptomatic patients with ADPKD. Levey et al formally examined this question using decision analysis . Their analysis suggested that screening and prophylactic repair only increased life expectancy for patients younger than age 25.More recent data from large prospective studies suggest that the prevalence of aneurysm in asymptomatic patients with ADPKD is less than 10% .

The prevalence of asymptomatic ICA is 22% to 25% in family members of ADPKD patients who are known to have ICA. More recent estimates of surgical morbidity and mortality suggest a figure of 2% to 6%, rather than the 1% to 3% figure utilized in the initial analysis. These datas strengthens the argument against angiographic screening for the unselected ADPKD population. If, on the other hand, a highly sensitive and specific noninvasive screening test (greater than 80% and 85%, respectively) could define an individual ADPKD patient with a high probability of having an ICA, angiographic study and prophylactic repair of the lesion would confer a significant survival benefit . High resolution three dimensional magnetic resonance angiography (MRA) with time-of-flight image processing techniques probably meets these criterias and is the imaging modality of choice [52,53]. It carries no risk of

ionizing radiation, is noninvasive, and unlike computed tomography (CT) angiography does not use iodinated contrast, which may be nephrotoxic. If the population prevalence were 30% (that is, a positive family history of ICA), the positive predictive value of an MRA showing an ICA is 80%; therefore, in most patients with family histories of ICA who have a positive MRA, angiography would reveal an ICA. But patients with ADPKD appear to have an increased rate of neurologic complications due to cerebral angiography, so it is highly desirable to limit the number of studies . At present, no neurosurgical consensus exists on the appropriate treatment for small, asymptomatic KAs (less than 10 mm particularly for aneurysms larger than 5 mm . Data derived from the general population indicate that the main predictor of aneurysmal rupture is its size[54,55]. Wiebers and Torres advocate repeated MRA screening of known asymptomatic, small ICAs . They base their recommendation on data showing that there were no ruptures of 102 ICAs less than 10 mm in diameter over a mean followup period of eight years [56]. Juvela et al advocate prophylactic repair of any surgically accessible ICA, as long as the age and concurrent diseases of that patient do not increase the surgical risk . Three studies clearly document the formation and rupture of de-novo ICA in ADPKD patients with prior ICA rupture [57-59]. Data on long-term followup of known

incidental (discovered solely via screening) ICA in patients with ADPKD are very limited. In a recent study of 18 ADPKD patients, 15 asymptomatic, small (1.5—6.5 mm) ICAs were followed for a mean of 33 months using serial MRA examinations ; none of the aneurysms changed in size or ruptured, and no de-novo aneurysms formed. Autosomal-dominant polycystic kidney disease (ADPKD) patients with either PKD1 or PKD2 mutations are at risk for intracranial aneurysms. The efficacy of a screening program depends heavily upon the sensitivity and specificity of the screening modality, the prevalence of disease, and the potential benefit of a positive diagnosis.

DIAGNOSIS

The diagnosis of ADPKD in an individual with a positive family history relies on imaging testing. Counseling should be done before testing. Benefits of testing include certainty regarding diagnosis that may influence family planning, early detection and treatment of disease complications, and selection of genetically unaffected family members for living related donor renal transplantation The sensitivity of ultrasound to confirm a diagnosis of ADPKD in individuals who have a 50% a priori risk of having the disease by genetic linkage was studied by Ravine et al. Currently used criteria of bilateral cysts with at least

two in one kidney provides a sensitivity of 88.5% at age 15 to 29 years and 100% at 30 years of age and above. Less stringent criteria in subjects aged 15 to 29 years to establish a diagnosis of ADPKD for individuals at risk would be at least two renal cysts (unilateral or bilateral). More stringent criteria in those aged 30 to 59 years to establish a diagnosis is the presence of at least two cysts in each kidney. For at-risk individuals 60 years and older, at least four cysts in each kidney should be required. Other reviews of ADPKD have established less exact criteria to establish a diagnosis. By ultrasonography cysts are round or oval, echolucent, thin-walled, clearly delineated structures with smooth contours exhibiting sharply demarcated posterior walls and sound wave amplification behind the cysts as well as lateral extinction of the sound wave (lateral shadowing).

These sonographic criteria are not applicable to more sensitive imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI).There are two types of potential misdiagnosis. In very young individuals, the diagnosis may be missed because the renal parenchyma presents with a hyperdense texture only, but even at this early stage hilar and intrarenal vessels exhibit unusually strong vascular reflexes. Occasionally a CT scan permits detection of very

small incipient cysts in such cases. While magnetic resonance imaging (MRI) and computed tomography scanning are perhaps slightly more sensitive for detecting cysts, the cost of these procedures is much greater than ultrasonic examination and less widely available. At present, ultrasound should be used preferentially for diagnosis.

At present, in most persons with a 50 percent risk of autosomal dominant polycystic kidney disease, imaging techniques are the only mode of reaching a diagnosis before symptoms appear. In such persons a negative ultrasonographic study during early adult life indicates that the likelihood of inheriting a PKD1 mutation is small. In the few who inherit a non-PKD1 mutation for polycystic kidney disease, renal failure is likely to occur relatively late in life.

With modern advances in genetics, the DNA sequence of individual patients can be determined. However, these expensive tests are not widely utilized at the present time, except in unusual cases to confirm a questionable diagnosis or to exclude a possible organ donor in a patient with a family history of ADPKD .

MANAGEMENT

A patient with ADPKD managed by internists should have careful blood pressure control and control of other cardiovascular risk factors such as tobacco smoking, hyperlipidemia, body weight management, and aggressive control of diabetes if present.

Pain in patients with polycystic kidney disease can be both acute and chronic, often being difficult to manage in patients with more severe symptoms. However, with the utilization of a variety of traditional and recently available pain management techniques, pain can be managed effectively in most of these patients. In addition, patients can be taught "how to live with their pain" since permanent cure of chronic pain is often not a realistic goal. Behavioral modification approaches can help patients adapt to chronic pain so as to not interfere with their lifestyle. ADPKD patients may suffer complications such as infected cysts, cyst rupture/hemorrhage, and nephrolithiasis that often cause crippling acute renal pain.

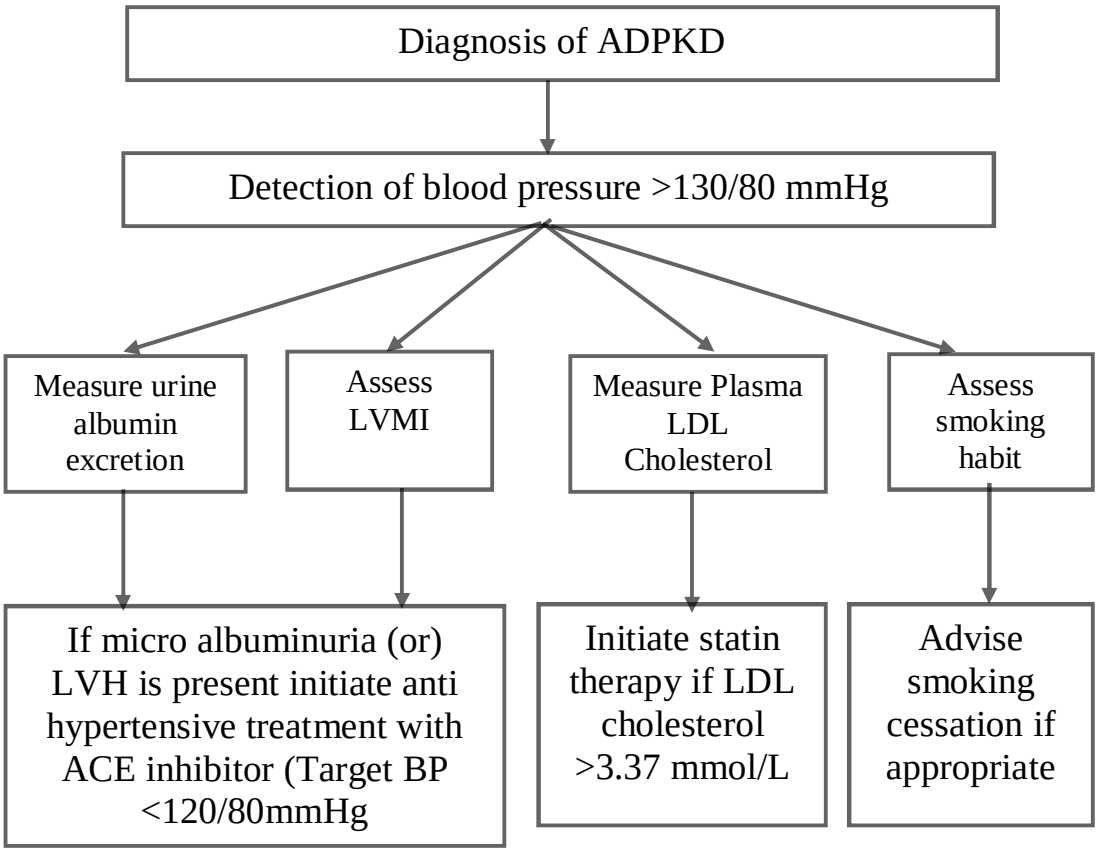
The antibiotic therapy of UTI has been adapted according to urine cultures and oral administration of antibiotics with good intracyst penetration such as cotrimoxazole or preferably a fluoroquinolone such as ciprofloxacin, had been choosen for long term prophylaxis. Highly

ionized water-soluble drugs may have a low ability to penetrate this barrier, whereas the use of nonionized lipid soluble antibiotics generally can improve delivery into the cyst. Therefore, many antibiotics such as the penicillins, cephalosporins, and aminoglycosides that have traditionally been first line therapy for severe UTIs may not be effective in ADPKD. Drugs with good cyst-penetrating ability, such as clindamycin, trimethoprim-sulfamethozazole, metronidazole, and fluoroquinolones may be more effective. However, it is possible that even these may not be effective, necessitating surgical drainage of the infected cysts.

The optimal treatment of patients with ADPKD should include a blood pressure goal of 120/80 mmHg and the initiation of early RAAS inhibition if microalbuminuria or LVH is present. Furthermore, management of other cardiovascular risk factors, including smoking and dyslipidemia, is extremely important. The diagnosis of hypertension in ADPKD is often made late. Uncontrolled blood pressure increases the morbidity and mortality from valvular heart disease and aneurysms, and increases the risk of proteinuria, hematuria, and a faster decline of renal function. The presence of hypertension also increases the risk of fetal and maternal complications during pregnancy.

MANAGEMENT

APPROACH TO ASSESSMENT OF CARDIOVASCULAR RISK FACTORS & MANAGEMENT IN PATIENTS WITH ADPKD



LVMI- Left Ventricular Mass Index

EMERGING TREATMENT STRATEGIES

Based on natural history studies involving MRI determinations of annual increases in cyst volume, therapeutic trials of agents shown to bebeneficial in animal models of cystic disease are anxiously awaited.

Clearly, no single unifying mechanism relates the normal functions of the polycystin proteins to the pathology that develops in their absence. It is, however, probably safe to assert that the progression of cystic disease is predicated upon perturbations in two fundamental processes. The epithelial cells that line cysts appear to proliferate excessively and these cells secrete rather than absorb fluid and electrolytes. . Thus, many current efforts aimed at developing small molecule therapies for ADPKD target one or the other of these derangements. Because fluid secretion into cyst lumens is mediated, at least in part, by apical CFTR chloride channels and is stimulated by cAMP, both of these factors may constitute promising molecular targets.

The CFTR inhibitor compound CFTRinh172 appears to substantially slow cyst expansion . Inhibition of a basolateral potassium channel whose activity is required to maintain the electrochemical potential that drives chloride and fluid secretion is also being explored

as an approach to blocking cyst fluid accumulation. Antidiuretic hormone (ADH), acting through the V2 vasopressin receptor, is a major stimulant of cAMP production in the collecting tubule of the kidney. Tolvaptan, a V2 receptor antagonist, dramatically reduces cyst progression in mouse models of ADPKD. Ocreotide, a somatostatin analogue, also inhibits cAMP accumulation in several cell types and has produced intriguing results in animal models.

The observation that inappropriately high mTOR activity may contribute to the excessive growth and proliferation that characterize cystic tissue has prompted investigations into the utility of mTOR inhibitors ,Sirolimus in the setting of ADPKD. Animal studies have suggested dramatic beneficial effects, although recent clinical trial data suggest that these results are not borne out in ADPKD patients, and the side effects of chronic mTOR inhibition may be substantial enough to further limit its potential utility.

Other efforts have directly targeted the regulation of mitosis. Roscovitine, an anti-proliferative drug that blocks Cdks, dramatically slows cyst formation in at least some animal models of PKD. Additional emerging potential therapies are directed at other interesting targets. These include triptolide, a compound derived from a traditional Chinese

herbal therapy; pioglitazone, a PPAR-alpha agonist; and Genz-123346, which blocks glycosyl ceramide synthesis. The connection between these compounds' molecular targets and the pathological processes involved in ADPKD remain to be determined. Further exploring these molecules, however, may reveal promising new pharmacological approaches to treating this disease and may also shed light on as-yet-undiscovered connections between the polycystin proteins and a variety of cellular signaling and metabolic pathways.

Stabilization or a decrease in cyst volume will be the outcome measure used to gauge therapeutic efficacy in these ongoing clinical trials . If these therapies prove useful, screening of individuals at risk for ADPKD will become more important because early initiation of such therapy may prevent the progression to chronic kidney disease or even end-stage renal failure.

Materials and Methods

MATERIALS AND METHODS

SETTING

Patients attending the Department of Internal Medicine and Department of Nephrology, Madras medical college and Government General hospital, Chennai.

COLLABORATION DEPARTMENTS

Institute of Internal Medicine

Department of Nephrology

ETHICAL APPROVAL

Institutional Ethical committee approved the study

STUDY DESIGN

Single center; Non randomized cross sectional study

DURATION

November 2009 - October 2010

SELECTION OF PATIENTS

Inclusion criteria

Both symptomatic and asymptomatic patients with autosomal dominant polycystic kidney disease meeting imaging criteria.

Exclusion criteria

1. Patients with simple cystic kidney disease
2. Patients not meeting imaging criteria

SAMPLE SIZE

In the study period of 1 year among patients seen under the Department of Internal Medicine and Nephrology, after applying inclusion criteria ,39 patients were included in this study.

CONSENT

All participants gave informed consent.

METHODOLOGY

Patients who were included in this study were asked for the history of abdominal &flank pain, abdominal distension, hematuria, fever with rigors &chills, passage of stones, oliguria, bilateral leg swelling, jaundice, chest pain, palpitation, breathlessness, headache, giddiness ,stroke, family history, diabetes, hypertension, smoking, alcohol consumption. The information was entered based on the proforma prepared. Patients were subjected to Renal function tests, Liver function tests, Urine culture, Electrocardiogram, Chest x-ray, Echocardiogram, Ultrasonogram abdomen/ Computed tomography abdomen and Magnetic resonance angiogram brain.

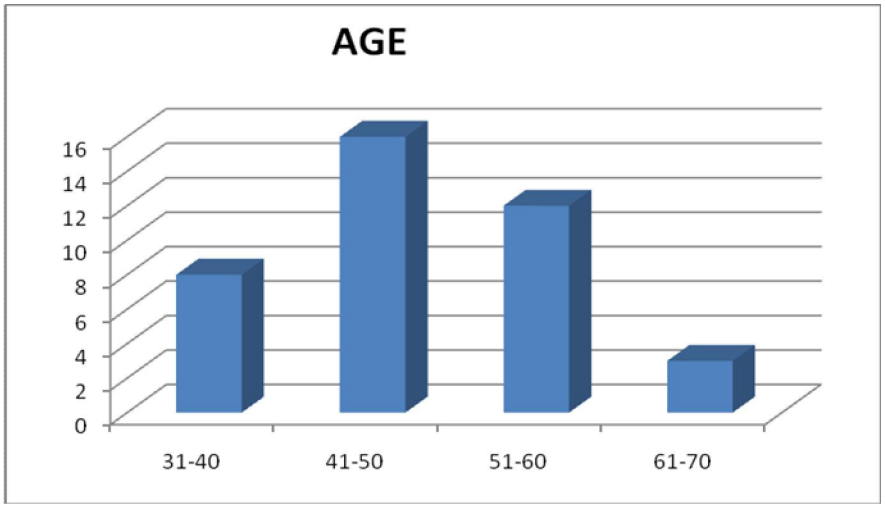
STATISTICAL ANALYSIS

Excel worksheet / Fisher’s exact test

CONFLICT OF INTEREST

None

Observations and Results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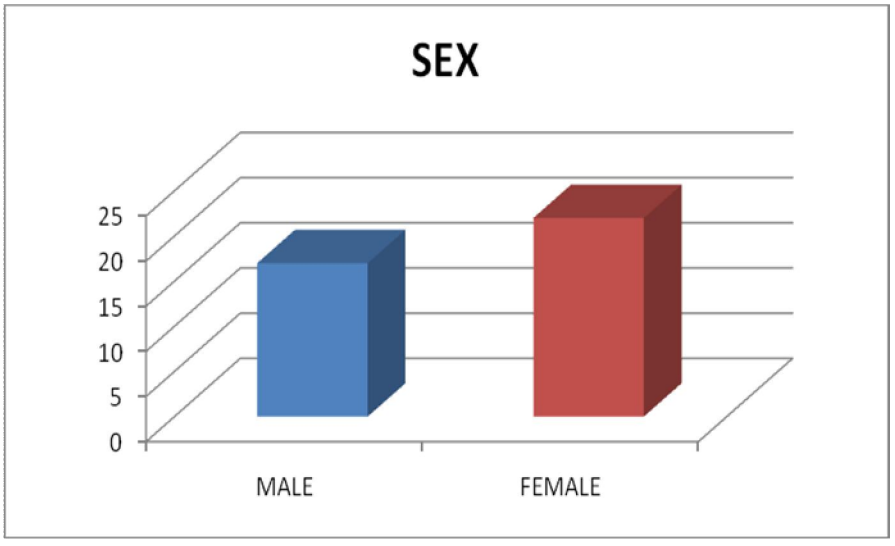
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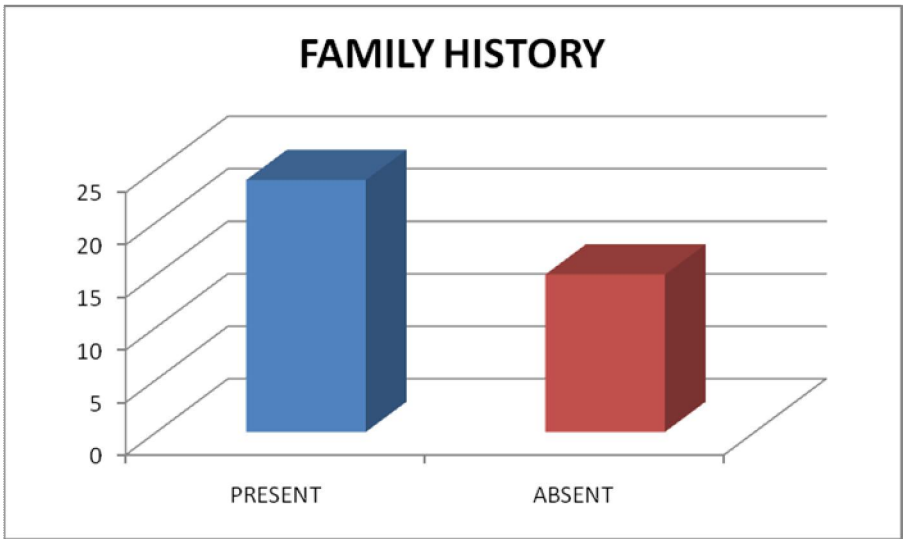
FEMALE


FAMILY HISTORY
25
20
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PRESENT
ABSENT

RESULTS

DEMOGRAPHIC ANALYSIS

AGE DISTRIBUTION

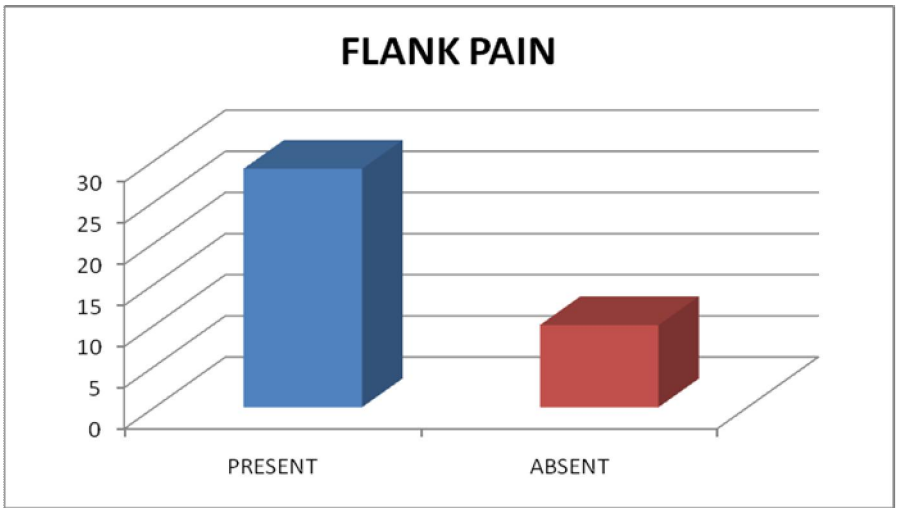
AGE	FREQUENCY	PERCENTAGE
31-40	8	20.5
41-50	16	41.0
51-60	12	30.8
61-70	3	7.7

SEX

SEX	FREQUENCY	PERCENTAGE
MALE	17	41.4
FEMALE	22	58.6

FAMILY HISTORY

FAMILY HISTORY	FREQUENCY	PERCENTAGE	
PRESENT	24	61.5	P<0.001 Significant
ABSENT	15	38.4	


FLANK PAIN
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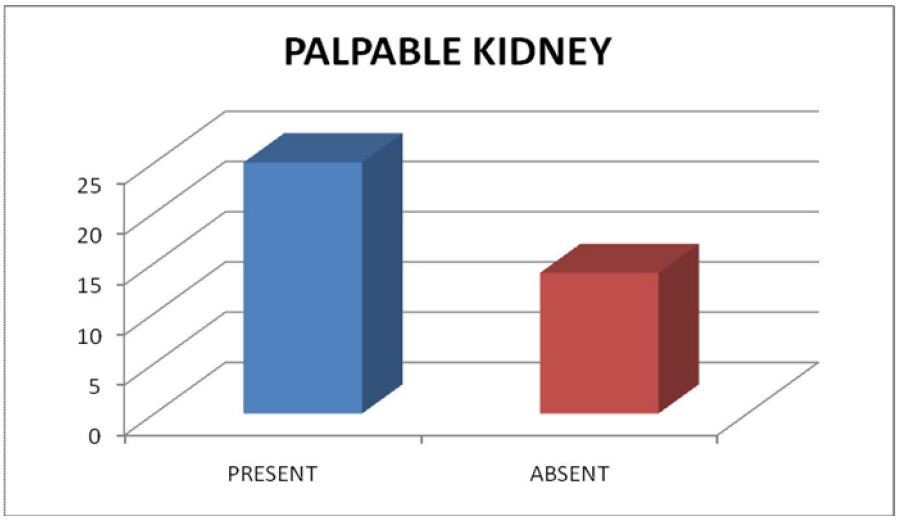
PALPABLE KIDNEY
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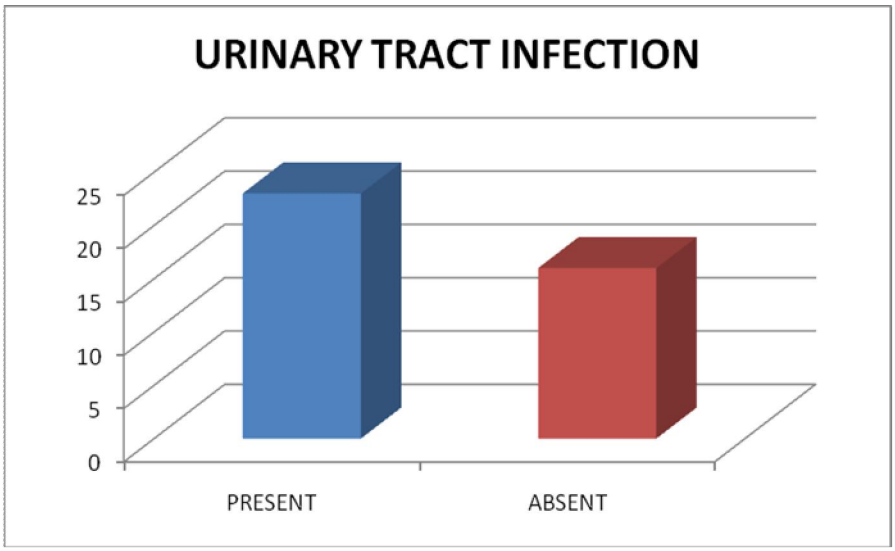
URINARY TRACT INFECTION
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PRESENT
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FLANK PAIN

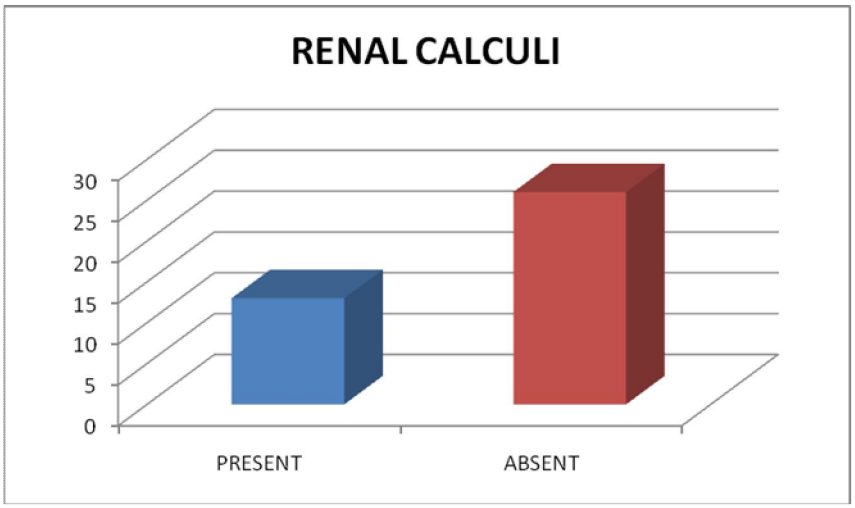
FLANK PAIN	FREQUENCY	PERCENTAGE	
PRESENT	22	56.4	P=0.0322 Significant
ABSENT	17	43.6	

PALPABLE KIDNEY

PALPABLE KIDNEY	FREQUENCY	PERCENTAGE	
PRESENT	11	28.2	P=0.1918 Not significant
ABSENT	28	71.8	

URINARY TRACT INFECTION

URINARY TRACT INFECTION	FREQUENCY	PERCENTAGE	
PRESENT	23	65.5	P=0.001 Significant
ABSENT	16	34.5	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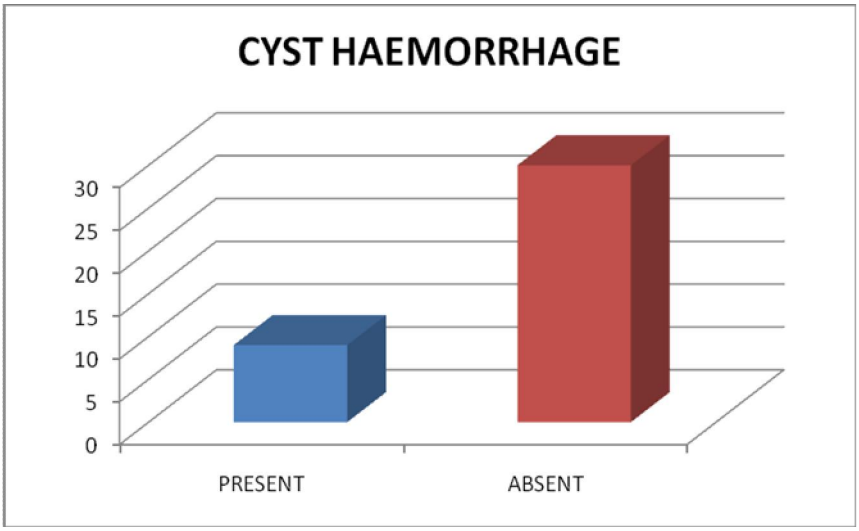
CYST HAEMORRHAGE
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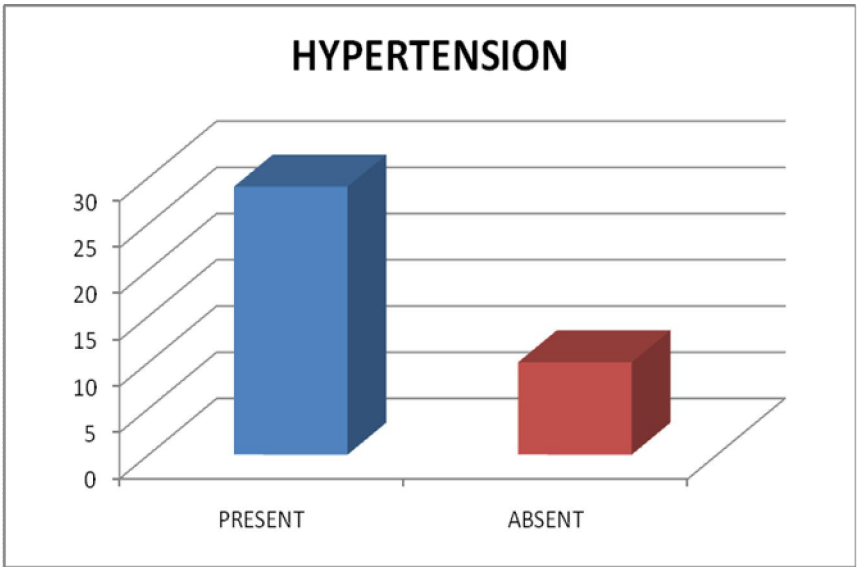
PRESENT
ABSENT


HYPERTENSION
30
25
20
15
10
5
0
PRESENT
ABSENT

RENAL CALCULI

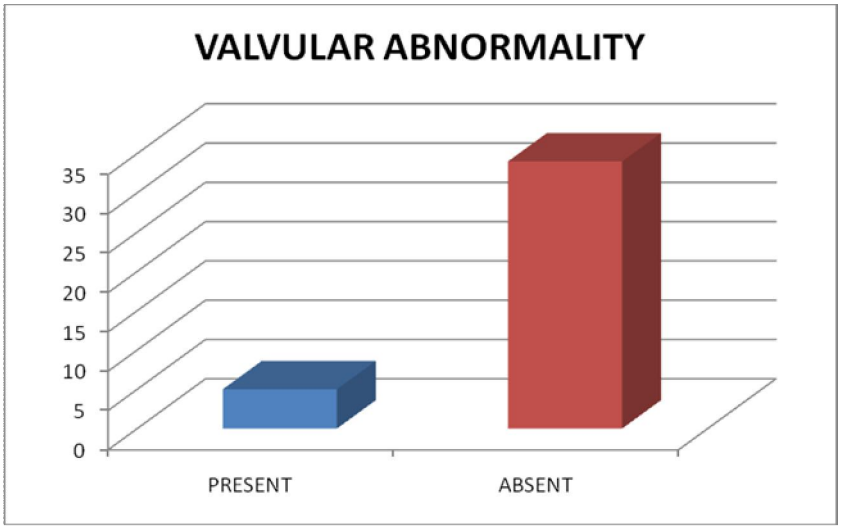
RENAL CALCULI	FREQUENCY	PERCENTAGE	
PRESENT	15	38.5	P=0.7734 Not significant
ABSENT	24	61.5	

CYST HEMORRHAGE

CYST HEMORRHAGE	FREQUENCY	PERCENTAGE	
PRESENT	9	23	P=0.0145 Significant
ABSENT	30	77	

HYPERTENSION

HYPERTENSION	FREQUENCY	PERCENTAGE	
PRESENT	29	74.3	P=0.0001 Significant
ABSENT	10	25.6	


VALVULAR ABNORMALITY
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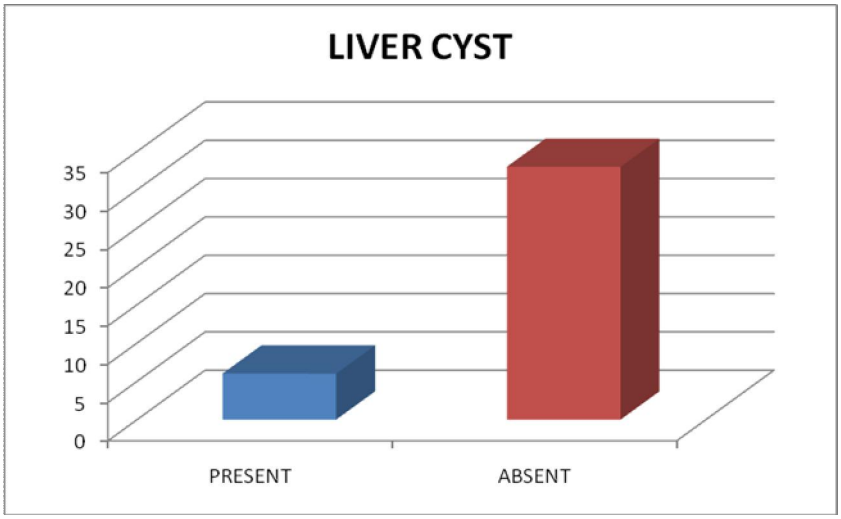
PRESENT
ABSENT


LIVER CYST
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30
25
20
15
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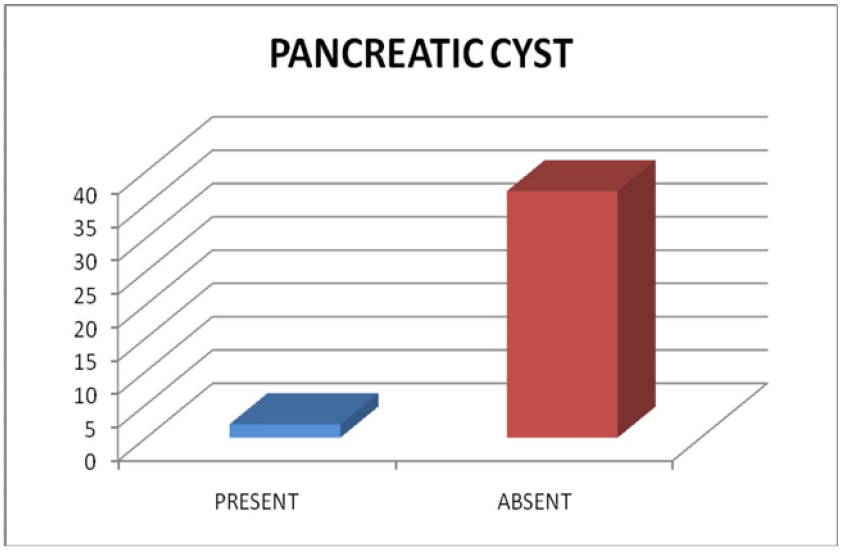
PRESENT
ABSENT


PANCREATIC CYST
40
35
30
25
20
15
10
5
0
PRESENT
ABSENT

ECHOCARDIOGRAPHIC FINDINGS

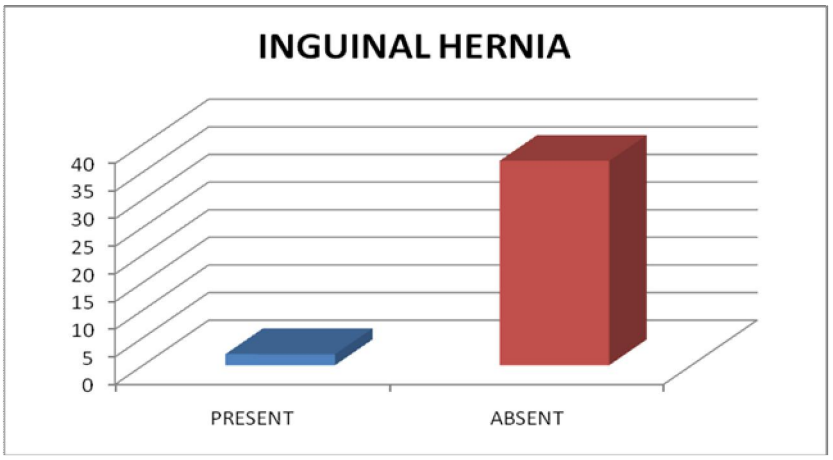
ECHOCARDIOGRAPHIC FINDINGS	FRE-QUENCY	PERCENT-AGE	P=0.6132 Not significant
PRESENT	5	12.8	
ABSENT	34	87.2	

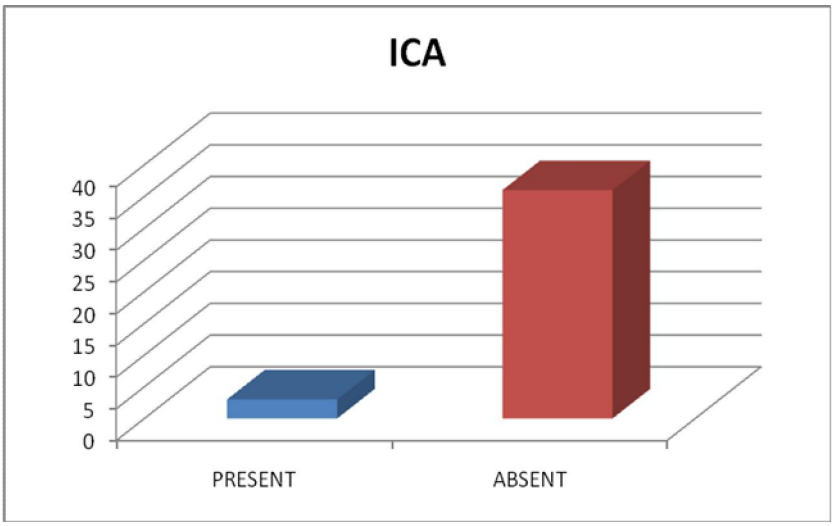
LIVER CYST

LIVERCYST	FRE-QUENCY	PERCENT-AGE	P=0.8040 Not significant
PRESENT	6	15.4	
ABSENT	33	84.6	

PANCREATIC CYST

PANCREATIC CYST	FREQUENCY	PERCENTAGE	P=0.7278 Not significant
PRESENT	2	5.1	
ABSENT	37	94.9	


INGUINAL HERNIA
40
35
30
25
20
15
10
5
0
PRESENT
ABSENT


ICA
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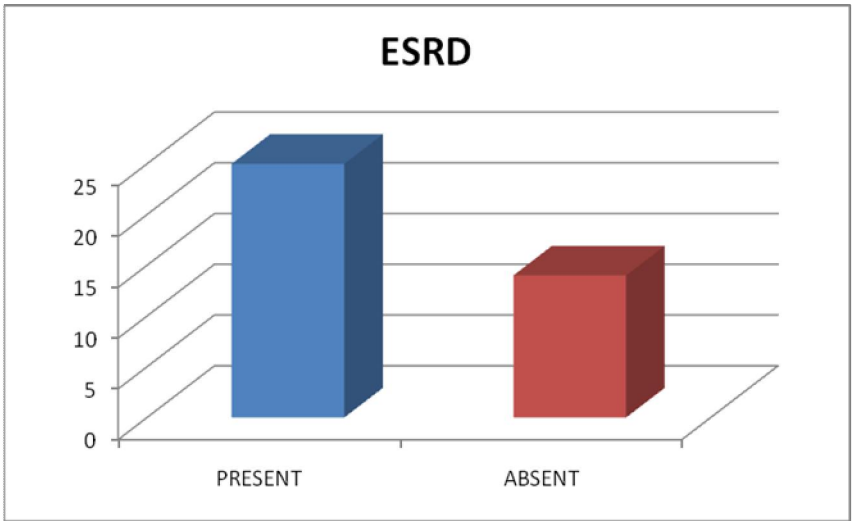
ESRD
25
20
15
10
5
0
PRESENT
ABSENT

INGUINAL HERNIA

INGUINAL HERNIA	FREQUENCY	PERCENTAGE
PRESENT	2	6.9
ABSENT	37	94.9

INTRACRANIAL ANEURYSM

INTRACRANIAL ANEURYSM	FREQUENCY	PERCENTAGE	P=1.000 Not significant
PRESENT	3	7.7	
ABSENT	36	92.3	

ENDSTAGE RENAL DISEASE (ESRD)

ESRD	FREQUENCY	PERCENTAGE	P=0.1445 Not significant
PRESENT	25	64.1	
ABSENT	14	35.9	

Discussion

DISCUSSION

AGE

Majority of patients in our study was in the age group of 41-50.

SEX

Females were predominantly affected than males.

FAMILY HISTORY

Family history of ADPKD was absent in 38.4% of patients in our study which was statistically significant. However Lieske et al found that 10% of patients had no family history of ADPKD. This significant difference may be due to illiteracy and unawareness of the disease among the patients in our study.

NEPHROLITHIASIS

Renal stones are a frequent complication of ADPKD and are reported to occur in 11 to 34% of patients. Idrizia et al described nephrolithiasis in 42% of patients. In our study, renal stones were present in 38.5% (n=15)of patients of which ten were female and five were male patients. However Torres et al found that incidence of

nephrolithiasis was equal between men and women in patients with normal renal function.

FLANK PAIN, URINARY TRACT INFECTION(UTI), CYST HAEMORRHAGE

Delaney et al studied 53 symptomatic adults for a mean followup of 12 years, of which flank pain was present in 30% of patients and symptomatic UTI in 19% of patients. In our study, atleast one episode of UTI and flank pain is present in 66.7% of patients.

Gabow et al described that gross hematuria was the presenting symptom in 15-20% of patients and occurs atleast once in 30-50% of patients with ADPKD. Gross hematuria is usually secondary to renal cyst rupture into the renal pelvis. Infection,segmental renal infection and passage of renal calculi also cause gross hematuria in ADPKD. Isolated cyst infections were detected by negative urine culture and absence of white blood cell casts in urinary sediment. In our study cyst hemorrhage was found in 23% of patients.

Milutinovic J et al studied clinical manifestations of 57 subjects aged more than 50 years who had inherited ADPKD gene. Diagnosis was made in 32/57 (56%) of patients, clinical features were found in 31/57(55%), of which 47% had back pain and abdominal pain,

symptoms consistent with UTI was present in 41% of patients, hematuria and ESRD in 31% and 47% of patients respectively. Statistically significant difference was not found in frequency of any of the manifestation of ADPKD except UTI which was higher in women (53%) than in men (27%).

PALPABLE KIDNEY

Delaney VB et al reported that palpable kidneys were found in 15% of 53 adult symptomatic ADPKD patients. In our study 28.2% of patients had palpable kidney. This significant difference could be due to smaller sample size in our study.

EXTRARENAL MANIFESTATION

CARDIOVASCULAR MANIFESTATIONS

Kenneth F, Hossack et al compared the prevalence of cardiac abnormalities among 163 patients with ADPKD, 130 unaffected family members and 100 control subjects in three groups. The prevalence of Mitral valve prolapse was 26%, 14% and 2% respectively. He also found a higher prevalence of mitral incompetence (31%,14%,9% respectively), tricuspid incompetence (15%,7% and 4% respectively) and tricuspid valve prolapse (6%, 2% and 0% respectively).

Stephen B Humap et al found that echocardiography revealed no difference in left ventricular mass index nor prevalence of mitral valve prolapsed.

Ecder T,Schrier RW et al proposed that cardiovascular problems are a major cause of morbidity and mortality in patients with ADPKD. Hypertension is an early symptom of ADPKD and occurs in 60% of patients before renal function has deteriorated. Hypertension is associated with increased rate of progression to ESRD and is the most important potentially treatable variable in ADPKD. Left ventricular hypertrophy(LVH) ,which is a powerful independent risk factor for cardiovascular morbidity and mortality, also occurs frequently in patients with ADPKD. Both hypertension and LVH have important role in cardiovascular complications in these individuals. Morever biventricular diastolic dysfunction, endothelial dysfunction, increased carotid intima-media thickness and impaired coronary flow velocity reserve are present even in young patients with ADPKD who have normal blood pressure and well preserved renal function.

In our study we reported 29 out of 39 patients having hypertension irrespective of the presence of ESRD which was stastically significant.

Chapman et al reported that 48% of hypertensive patients with ADPKD had Left ventricular Hypertrophy (LVH) and increased left ventricular mass index (LVMI), which is associated with poor renal and overall outcome.

In our study, out of 39 patients 5 patients (12.8%) had atleast one valvular manifestation. Irrespective of valvular abnormalities 15 had echocardiagraphic finding of LVH.

Leier et al reported that 18% of patients had one or more cardiovascular abnormalities. Hossack KF et al have found that 26% , 31% 8%,15%,6% of patients had mitral valve prolapse, mitral incompetence, aortic incompetence, aortic incompetence, tricuspid incompetence and tricuspid valve prolapse respectively. Timio M et al reported that in a study of 228 patients of ADPKD over a 10 year followup in a five generation kindred 25% had mitral valve prolapse, 30% had mitral incompetence, 5% had tricuspid valve prolapsed and 19% had aortic regurgitation. In our study out of 29 patients, 15 patients had LVH irrespective of ESRD, 1 had tricuspid aortic valve, 2 had mitral regurgitation,1 had mitral valve prolapsed and 1 had sigmoid septum.

LIVER CYSTS

Kumar VS et al reported that 18.5% of 92 ADPKD patients had liver cysts. Liver cysts were more common in men and were mostly multiple. In our study out of 39 patients 6 (15.4%) had liver cyst.

PANCREATIC CYSTS

Torra et al had reported that approximately 9% of patients with ADPKD had pancreatic cysts. Complications due to pancreatic cyst are extremely rare but a case of chronic obstructive pancreatitis due to pancreatic cyst has been reported by Malka D et al. Our study has revealed that 5.1% of patients with ADPKD had pancreatic cyts of which none of them developed complications.

INGUINAL HERNIA

Non cystic extrarenal manifestations like abdominal hernia is usually prevalent in ADPKD. This is due to underlying defect in extracellular matrix production with variable penetrance. In our study, only 6.9% of patients presented with inguinal hernia.

INTRACRANIAL ANEURYSMS

P M Ruggieri et al done a study for occult intracranial aneurysms in polycystic kidney disease by screening with MR angiography.

Ninety-three patients with PCKD were screened for aneurysms with spin-echo parenchymal magnetic resonance (MR) imaging and three-dimensional time-of-flight MR angiography. Thirteen aneurysms, found in 10 patients, were 7 mm or smaller in largest dimension; 11 of these aneurysms were saccular. Conventional arteriograms, obtained in six patients, helped confirm the MR angiographic findings. The best estimates of prevalence of aneurysms were 11.7% in the study group (n = 93) and 25.8% in patients with a family history of aneurysms (n = 6).

Arlene B .chapman et al reported that four of the 88 subjects in whom the radiologic studies were successfully completed had intracranial aneurysms (4 percent; 95 percent confidence interval, 0.1 to 9 percent), as compared with the prevalence of 1 percent reported for an angiographic study of the general population. In our study we reported ICAs in 3 out of 39 patients contributing to 7.7%.out of these one patient was symptomatic and presented as subarachnoid hemorrhage even before the diagnosis of ADPKD. Lozano AM et al reported aneurysmal rupture at a younger age in patients with ADPKD (mean age around 40%) .

Conclusion

CONCLUSION

1) Urinary tract infection, especially in females, is the most common clinical manifestation in ADPKD. Most common organism was found to be enterobacteriaceae.

2) Liver cysts are the most common extrarenal manifestation in ADPKD.

3) Renal ultrasound screening of young hypertensive individuals should be considered when searching for causes of secondary hypertension.

4) In evaluating every case of SAH ,normo or hypertensive ,it is mandatory to rule out ADPKD.

5) Hypertension can manifest in patients with ADPKD even before the onset of end stage renal disease.

6) Multisystem involvement in ADPKD reflects the systemic nature of polycystic kidney disease and supports the hypothesis that the disorder involves a defect in ECM(Extracellular matrix) and the various manifestations are an expression of that defect.

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Study Proforma

STUDY PROFORMA

Name :

Age/Sex :

Address :

Annual Income :

Socio economic class :

MRD No :

Study id no :

CLINICAL DATA

HISTORY:

Presenting complaints:

Flank pain, hematuria, abdominal distension, giddiness, headache, jaundice, Palpitations, chest pain, dyspnoea, fever,syncope,seizures,pedal edema

Past History:

Diabetes mellitus, systemic hypertension, liver disease, cardiac disease.

Treatment history: (including any surgeries)

Personal history:

Smoking, alcohol, menstrual complaints for female patients.

Family history:

Seizures,CVA

PHYSICAL EXAMINATION:

General examination:

General well being, dyspnoea, pallor, jaundice, pedal edema.

Vital signs:

Pulse rate: BP:

Respiratory rate: Temp:

JVP:

Systemic examination:

CVS:

RS:

ABDOMEN:

{masses, hepatosplenomegaly, ascites }

LABORATORY DATA

PRELIMINARY INVESTIGATIONS:

TEST	RESULT
Fasting blood sugar	
Blood urea, serum creatinine	
CBC	
Serum bilirubin	
Direct/ indirect bilirubin	
AST/ALT	
SAP	
Total protein	
Serum albumin/ globulin	
Urine routine	
CXR PA View	
ECG	
ECHO	
USG Abdomen/ CT	

SPECIAL INVESTIGATIONS:

MR Angiography:

INFERENCE:

Abbreviations

ABBREVIATIONS

ADPKD	-	Autosomal Dominant Polycystic Kidney Disease
LVMI	-	Left ventricular Mass Index
PC_1	-	Polycystin 1
PC_2	-	Polycystin 2
UIA	-	Unruptured Intracranial aneurysm
RAAS	-	Renin Angiotensin Aldosterone System
LVH	-	Left ventricular hypertrophy
ESRD	-	End Stage Renal Disease
GFR	-	Glomerular Filteration Rate
m TOR	-	Mammalian Target of Rapamycin
cdk	-	Cyclin Dependent Kinases
TSC	-	Tuberous Sclerosis Complex

Master Chart

MASTER CHART

Sl.No.	Name	Age	Sex	Family h/o	HT	Echo	Liver cyst	Panc cyst	Ing hernia	ICA	Flank pain	Pal kidney	UTI	Calculi	Cyst hge	ESRD
1	Sahadev	35	MALE	NO	YES	LVH	NO	NO	NO	NO	NO	YES	NO	NO	NO	YES
2	Kalathee	46	MALE	NO	YES	LVH,TAV	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES
3	Natarajan	45	MALE	YES	YES	NORMAL	NO	YES	NO	NO	YES	NO	YES	NO	NO	YES
4	Devendran	35	MALE	YES	YES	LVH	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
5	Loganath	44	MALE	NO	YES	NORMAL	NO	NO	NO	NO	YES	YES	YES	YES	NO	YES
6	Muthulax	43	FEMALE	NO	YES	NORMAL	NO	NO	NO	NO	NO	NO	YES	NO	NO	YES
7	Lakshmi	45	FEMALE	YES	YES	LVH	YES	NO	NO	NO	YES	NO	YES	NO	NO	YES
8	Rahman	54	MALE	NO	YES	MR	NO	NO	NO	NO	YES	YES	YES	NO	NO	YES
9	Lakshmi	55	FEMALE	YES	YES	NORMAL	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES
10	Ramakrish	55	MALE	YES	YES	sigmoidseptum	NO	NO	NO	NO	YES	YES	YES	NO	NO	YES
11	Packiriam	53	FEMALE	YES	NO	NORMAL	NO	NO	NO	YES	NO	YES	NO	NO	NO	NO
12	Thiruppal	40	FEMALE	YES	YES	LVH	YES	NO	NO	NO	YES	YES	YES	YES	NO	YES
13	Anbazhag	50	MALE	NO	NO	LVH	NO	NO	NO	NO	YES	YES	YES	YES	NO	YES
14	Renuka	47	FEMALE	YES	yes	NORMAL	YES	NO	NO	NO	YES	YES	NO	NO	NO	NO
15	Dhanam	48	FEMALE	NO	YES	NORMAL	YES	NO	NO	NO	YES	NO	YES	NO	NO	YES
16	Pattammal	60	FEMALE	NO	NO	NORMAL	NO	NO	NO	NO	YES	NO	YES	NO	NO	NO
17	Tamilarasi	43	FEMALE	YES	NO	NORMAL	NO	NO	NO	NO	NO	NO	NO	YES	YES	NO
18	Kuttyamma	46	FEMALE	YES	YES	LVH	NO	NO	NO	NO	YES	NO	YES	YES	NO	YES
19	Balakrishnan	59	MALE	YES	YES	LVH	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
20	Palanisamy	58	MALE	NO	NO	NORMAL	NO	NO	NO	NO	NO	NO	YES	NO	YES	NO
21	Mani	37	MALE	YES	NO	NORMAL	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO
22	Raman	49	MALE	NO	YES	LVH	NO	NO	NO	NO	YES	YES	NO	NO	NO	YES
23	Shanmugham	66	MALE	YES	YES	MVP	NO	NO	NO	NO	NO	NO	YES	NO	NO	YES
24	Sulochana	36	FEMALE	YES	YES	LVH	NO	NO	NO	NO	NO	NO	YES	YES	NO	YES
25	Rohini	51	FEMALE	YES	NO	NORMAL	NO	NO	NO	NO	YES	NO	NO	YES	NO	NO
26	Kumariamma	64	FEMALE	YES	YES	NORMAL	no	NO	NO	NO	NO	NO	NO	YES	YES	NO
27	Renuka	31	FEMALE	YES	YES	LVH	NO	NO	NO	NO	YES	NO	YES	NO	NO	NO
28	Devasaga	50	MALE	YES	YES	LVH	NO	NO	NO	NO	YES	YES	YES	YES	NO	YES
29	Abraham	45	MALE	YES	NO	NORMAL	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
30	Pushpa	70	FEMALE	YES	YES	LVH	NO	NO	NO	NO	NO	NO	YES	YES	NO	YES
31	Maryamma	60	FEMALE	NO	YES	LVH	NO	NO	NO	NO	YES	NO	YES	NO	NO	YES
32	Kannamm	43	FEMALE	YES	YES	NORMAL	NO	NO	NO	YES	NO	NO	YES	NO	NO	YES
33	Thangadu	37	MALE	YES	NO	NORMAL	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO
34	Fathima	42	FEMALE	NO	YES	NORMAL	n0	NO	NO	NO	YES	NO	YES	NO	NO	YES
35	Kullammal	53	FEMALE	YES	YES	MR	YES	NO	NO	NO	NO	NO	YES	YES	NO	YES
36	Raju	39	MALE	NO	YES	NORMAL	NO	NO	NO	NO	YES	NO	YES	YES	YES	NO
37	Mohana	56	FEMALE	NO	YES	NORMAL	NO	NO	NO	NO	YES	NO	NO	YES	YES	YES
38	Velamma	44	FEMALE	NO	YES	NORMAL	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO
39	Chinnaponn	54	FEMALE	YES	YES	LVH	NO	NO	NO	NO	YES	NO	NO	YES	NO	YES

Institutional Ethical Committee Approval

(33)

INSTITUTIONAL ETHICAL COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-600 003

Telephone 25363970
Fax 044 2535115
Dated : 12.05.2010

L.Dis.No.14597/ME5/Ethics Dean/MMC/2010

Title of the work : "A study of clinical profile and extra-renal manifestations in autosomal dominant Polycystic kidney Disease."

Principal Investigator : Dr. Hemalatha.S
Designation : PG in MD General Medicine
Department :
Madras Medical College & GGH, Ch-3.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 12th May 2010 at 2.p.m in Pharmacology Seminar Hall, Madras Medical College, Chennai -3

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
4. You should not deviate form the area of the work for which you applied for ethical clearance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulation of the institution(s).
7. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, MMC,CHENNAI

CHAIRMAN
IEC,MMC, CHENNAI

DEAN
MADRAS MEDICAL COLLEGE,
CHENNAI -3